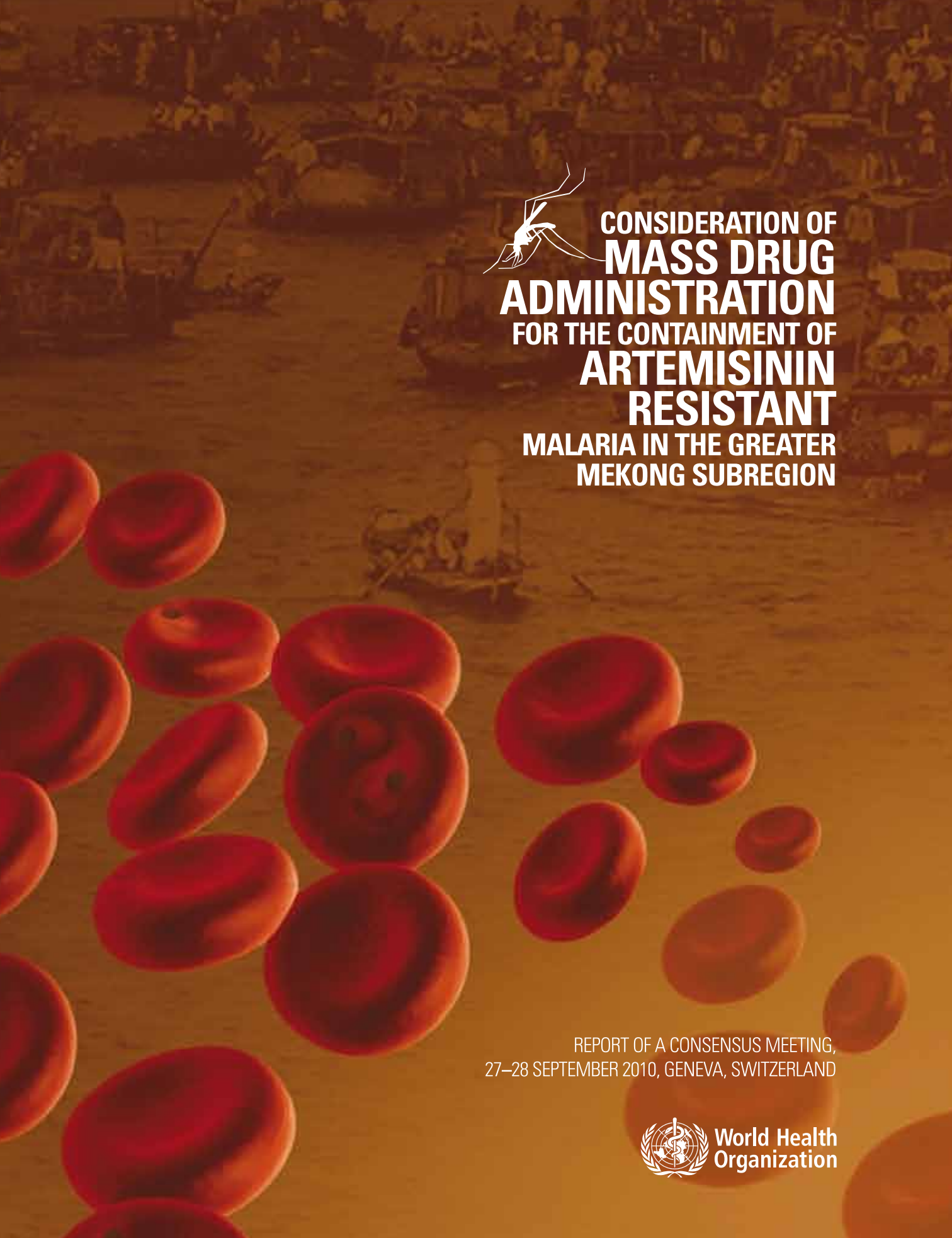

CONSIDERATION OF MASS DRUG ADMINISTRATION FOR THE CONTAINMENT OF ARTEMISININ RESISTANT MALARIA IN THE GREATER MEKONG SUBREGION

REPORT OF A CONSENSUS MEETING,
27–28 SEPTEMBER 2010, GENEVA, SWITZERLAND

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Abbreviations

ACT	artemisinin-based combination therapy
AP	atovaquone-proguanil
GPARC	Global Plan for Artemisinin Resistance Containment
G6PD	glucose-6-phosphate dehydrogenase
MDA	mass drug administration
PCR	polymerase chain reaction
WHO	World Health Organization

Executive summary

BACKGROUND

Plasmodium falciparum parasites in the border region of western Cambodia and eastern Thailand have shown evidence of resistance to artemisinins. This region has historically given rise to other drug-resistant strains of *P. falciparum* that eventually spread through Asia to Africa. A deterioration of the susceptibility of *P. falciparum* to artemisinins and the possibility that resistance will spread beyond the Greater Mekong subregion are significant threats to global strategies for the control and elimination of malaria. Since 2009, WHO and its partners have been working to contain artemisinin-resistant parasites at the Cambodia–Thailand border. This activity is referred to in this report as the 'artemisinin resistance containment project'.

Despite considerable achievements, the current strategies have their limitations (http://www.who.int/malaria/diagnosis_treatment/arcp/en/index.html). Mass blood surveys using the polymerase chain reaction (PCR) have shown that a significant number of people with *Plasmodium* parasitaemia are asymptomatic, and many have low parasite densities that cannot be detected by microscopy or rapid diagnostic tests. A potential approach for treating infections that escape diagnosis is mass drug administration (MDA).

MDA is the practice of treating a whole population within a given geographical area, irrespective of the presence of symptoms and without diagnostic testing. In general, WHO has discouraged MDA for routine malaria control because studies suggest that the impact on transmission is short-lived and because of the likelihood that it will result in selection for drug-resistant genotypes. However, given the tremendous public health risks associated with artemisinin resistance, MDA has been proposed for eliminating hard-to-reach parasite populations, such as those in asymptomatic patients. In September 2010, the WHO Global Malaria Programme convened a meeting of experts to evaluate the appropriateness of including MDA as part of the strategy to contain artemisinin-resistant parasites in the Greater Mekong subregion. This report reflects the discussions, conclusions and recommendations of the expert group.

DISCUSSION

Consideration of MDA for control of artemisinin resistance was triggered by operational research conducted as part of the artemisinin resistance containment project showing the limitations of existing diagnostic tests in populations with a high proportion of asymptomatic individuals and the difficult logistics of screening large populations. Mathematical modelling suggests that repeated rounds of MDA could lead to elimination of the artemisinin-resistant strain.

Nevertheless, the group also considered the challenges associated with introduction of MDA, which include the following:

- MDA might undermine current containment efforts;
- Recent unpublished data from the Myanmar–Thailand border and from Viet Nam suggest that the window of opportunity for contain-

ing or eliminating artemisinin resistance might have already closed;

- The high coverage rate required might be impossible to achieve;
- Mass administration of atovaquone-proguanil (AP) might lead to resistance to this antimalarial medicine;
- MDA might be considered unethical in view of the concerns about the safety of administering primaquine to a population in which the frequency of glucose-6-phosphate dehydrogenase (G6PD) deficiency is unknown;
- MDA might be socially and politically unmanageable.

The group also identified gaps in the evidence for MDA, including:

- poor resolution of the existing geographical borders of the artemisinin-resistant phenotype;
- unknown safety profile of primaquine in populations with a high prevalence of G6PD deficiency;
- unknown safety profile of AP and primaquine given in combination;
- unexplored optimization of the schedule of primaquine needed to kill gametocytes when administered with AP;
- unexplored optimization of the timing of MDA cycles;
- unknown effect of migration on MDA coverage rates and efficacy; and
- undefined indicators of the success of MDA operations.

The challenges and the gaps in evidence outlined above indicate that MDA has limitations. However, given the importance of containing and eliminating artemisinin resistance in the context of global malarial control, some consider that even an imperfect method is preferable to a more conservative response. MDA would alleviate the effort and expenses associated with diagnostic testing as well as the problems associated with misclassification. For these reasons, MDA is considered by some to be currently the best possible method for achieving elimination of artemisinin-resistant parasites.

RECOMMENDATIONS

Despite the many challenges that would have to be met in order to implement MDA effectively, the participants agreed that MDA should be considered for containing artemisinin-resistant parasites in the Greater Mekong subregion. With one exception, however, all the participants agreed that MDA should be considered only after certain research questions have been answered. It was agreed that implementation should begin with a pilot project. Given the amount of preparatory work required and the prerequisite that MDA be conducted during the low-transmission season, it was agreed that the earliest date for a pilot operation would be March 2012.

Introduction

The indications of artemisinin resistance in western Cambodia are alarming and demand action. The Greater Mekong subregion is historically the site of de novo emergence of resistance to antimalarial agents, which has subsequently spread through Asia to Africa. Loss of the artemisinin family of drugs to parasite resistance would severely impede global malaria control and elimination (Dondorp et al., 2010). Within the artemisinin resistance containment project, therefore, a massive effort has been made to stop the spread of the resistant strain. Despite the commendable achievements of the project, current activities may be limited in their ability to fully arrest the spread of resistance.

Given the enormous risks that the spread of artemisinin resistance pose to global malaria control, MDA has been proposed as an additional means for eliminating artemisinin-resistant parasites in the Greater Mekong subregion. MDA consists of administering antimalarial treatment to a large population, regardless of symptoms and without diagnostic testing. In order to evaluate the appropriateness of MDA as a containment measure, the WHO Global Malaria Programme convened a consensus meeting of malaria experts in Geneva in September 2010. The objectives of the meeting were to:

- review the benefits, risks, feasibility and practicalities of adding MDA to ongoing activities for the containment of artemisinin-resistant falciparum malaria in the Greater Mekong subregion;
- make specific recommendations on the use of MDA against *P. falciparum* in the context of containment and elimination of artemisinin-resistant falciparum malaria; and
- identify the research required before use of MDA in this context and region during the next two years.

This report provides a summary of the issues surrounding use of MDA for containing and eliminating a parasite strain. The participants weighed the benefits and risks of implementing MDA in this context. The outcome of the meeting was general acceptance of MDA as a potentially appropriate element of the artemisinin resistance containment strategy; however, lack of evidence precluded a recommendation for immediate implementation. Several research questions need to be answered before conclusions can be drawn about use of MDA for the containment of artemisinin resistance.

1. Background

1.1 EMERGENCE OF ARTEMISININ RESISTANCE

Slower parasite clearance times after treatment with artemisinin-based combination therapy (ACT) indicate reduced susceptibility to the otherwise rapidly acting artemisinins (Stepniewska et al., 2010). Evidence of slower parasite clearance times in response to artesunate and some ACTs has been emerging from western Cambodia since 2007 (Dondorp et al., 2009; Noedl, Socheat & Satimai, 2009; Rogers et al., 2009; WHO, 2010a). In a study conducted between June 2007 and May 2008, the median parasite clearance time was markedly slower in western Cambodia (84 h) than in western Thailand (48 h) ($P < 0.001$) (Dondorp et al., 2009). Neither increasing nor splitting the dose of artesunate improved the parasite clearance time in Pailin, although further research is needed to confirm these findings. As a result of these studies, positivity on day 3 (72 h after treatment) was used as an indication that the infection is due to a resistant parasite population.

The delayed clearance of parasitaemia is a concern because it could lead to increased gametocyte carriage, which facilitates the transmission of resistant parasites (Price et al., 1996; Mendez, Munoz & Plowe, 2006). Failure to kill gametocytes effectively is considered to have accelerated the spread of chloroquine resistance (Hallett et al., 2006). The short half-life of artemisinins combined with a resistance-driven extension of parasite clearance time increase the likelihood of propagating resistant parasites, both because of a failure to clear mature gametocytes and, especially, because of the emergence of young gametocytes deriving from the slow-to-clear parasite populations. In areas where prolonged clearance of asexual parasites prevails, resistant parasites may quickly dominate sensitive parasite populations, hastening the spread of resistant parasite strains.[1]

1.2 ARTEMISININ RESISTANCE CONTAINMENT PROJECT

The strategy for the containment of artemisinin resistance was developed by experts in 2008 in response to the early evidence of reduced parasite sensitivity in western Cambodia (WHO, 2008a). The core strategy was based on active case detection, improved case management with early diagnosis and treatment, and intensive vector control. Activities targeted both residential and mobile populations. The area was divided into two zones, a target and a buffer zone:

ZONE 1 (TARGET ZONE)	ZONE 2 (BUFFER ZONE)
• border areas where there is evidence of artemisinin resistance • activities aimed at local elimination of *P. falciparum* • Cambodia: 270 000 people in four provinces (Pailin and parts of Battambang, Pursat and Kampot) • Thailand: 110 000 people in the border areas (Trat and Chantaburi provinces)	• areas bordering zone 1 • intensified malarial control strategy • Cambodia: more than 4 million people living in nine provinces • Thailand: seven provinces with a population of nearly 7 million, about 150 000 of whom live in areas at risk for malaria

[1] Mathematical modelling using a population genetic approach suggests that use of gametocytocidal treatment might be counterproductive, as it might hasten the spread of resistance, once it has developed (Hastings, 2006).

The strategy required the active involvement and support of global and local stakeholders. The project's goal was to contain artemisinin-resistant *P. falciparum* parasites by removing selection pressure and reducing and ultimately eliminating falciparum malaria from the Cambodia–Thailand border area. During the first year, there was large-scale recruitment of staff for rapid procurement and roll-out of diagnosis, treatment and vector control in the containment zones of Cambodia and Thailand. This intense scaling-up of activities led to high coverage with bednets, at a ratio of one net per person in zone 1 and 100% coverage in the high-risk villages located in zone 2. Over 3000 village malaria workers who were recruited and trained for the project continue to provide free rapid diagnosis and treatment to residents of the target zones; they also reach out to mobile and migrant groups through education campaigns. National health statistics from Cambodia and Thailand show a significant decrease in malaria prevalence in containment zone 1 after implementation of these activities; however, it is unlikely that artemisinin-resistant parasites can be completely eliminated with the current strategy.

1.3 GLOBAL PLAN FOR ARTEMISININ RESISTANCE CONTAINMENT

The *Global Plan for Artemisinin Resistance Containment* (GPARC) is a high-level call to action to protect ACTs as an effective treatment for *P. falciparum* malaria. The plan was developed in 2010 by the WHO Global Malaria Programme in consultation with over 100 malaria experts. The plan builds on a strategy paper on antimalarial drug resistance prepared by the WHO Global Malaria Programme for the Roll Back Malaria Board as well as on lessons learnt from the artemisinin resistance containment project. One of the five objectives of the GPARC is to 'stop the spread of resistant parasites'. Several epidemiological and transmission-reduction tools are suggested for meeting this goal (WHO, 2011):

"In areas for which there is evidence of artemisinin resistance, an immediate, comprehensive response with a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites… Where artemisinin resistance is confirmed, national malaria control programmes may also consider a range of epidemiological or transmission-reduction tools, including focused screening and treatment, active case detection, mass screening and treatment or mass drug administration, in accordance with the latest evidence and guidelines."

The GPARC suggests four methods for reducing the parasite biomass dramatically and thereby reducing the potential pool of resistant parasites. Use of these tools is recommended on the condition that there is sufficient local experience or existing policy guidance. The GPARC recognizes that there is still *"insufficient evidence or technical consensus to recommend these interventions for resistance containment"*. A gametocytocidal agent could be used in any of the four approaches; however, the safety concerns related to administration of 8-aminoquinolines and screening for G6PD deficiency must be addressed. The four tools are described in more detail below.

Active case detection

Active case detection is the operation carried out by surveillance agents who visit every locality in a defined area at regular intervals (usually monthly during the transmission season), in order to detect fever cases through individual

house visits, and to test for malaria (and treat if positive) each suspected person so discovered (WHO, 2007). The defined areas are frequently selected based on an index case. This method is less resource-intensive than the following two methods but is unlikely to capture all unreported cases.

Mass screening and treatment

In mass screening and treatment, all the people in a broad geographic area are screened, regardless of whether they have symptoms of malaria. If the malaria diagnostic test demonstrates *Plasmodium* infection, then treatment is provided. The assumption on which this intervention is based is that most of the people who serve as an infectious reservoir have a high enough level of parasites in their blood to be detected at the time of screening. The main limitation of this approach is that it is resource-intensive and logistically challenging, especially in view of the lack of a field-ready, high-throughput, highly sensitive diagnostic test. Nevertheless, mass screening and treatment generate a wealth of information about the epidemiology of malaria that can be useful for further containment efforts.

Focused screening and treatment

Focused screening and treatment also involves screening all the people in a defined geographical area and providing treatment for those who test positive. It is operationally more feasible than mass screening and treatment, as, with a smaller target area, fewer resources are required. As focused screening and treatment are not delivered in all villages simultaneously, however, the strategy is unlikely to result in elimination of all resistant parasites. For this reason, it has been considered to be primarily an epidemiological research tool, which can provide valuable information on the characteristics of the population at risk. Focused screening and treatment may also be effective in reducing transmission, but this has yet to be confirmed.

Mass drug administration

MDA is perhaps the most radical of all of the tools proposed for the containment of artemisinin resistance. The WHO Global Malaria Programme's Technical Expert Group on Chemotherapy defined MDA as follows (WHO, 2010b):

..."every individual in a defined population or geographical area is required to take antimalarial treatment on a given day, in a coordinated manner, including the people who are not sick and not infected with malaria parasites at the time. Depending on the contraindications of the medicines used, pregnant women, young infants and other population groups are excluded from the campaign. The concept of MDA is based on the notion that if all people living in a given area could be effectively treated and rid of malaria parasites on a synchronized day, and the procedure repeated at intervals once or twice thereafter, the parasite reservoir of malaria in the area could be effectively reduced and eventually eliminated."

Although providing treatment to the entire population obviates the inherent problems of diagnostic testing, it introduces other complications. Poor evidence of sustained impact and the risks for selecting for drug-resistant mutants (von Seidlein & Greenwood, 2003) led the Technical Expert Group on Chemotherapy to discourage use of MDA as a routine malaria control strategy (WHO, 2010b):

"There is no evidence of long-term benefits to support MDA in large population groups. There is strong logic that MDA should select for drug

resistant genotypes of parasites. The larger the population of parasites that is targeted with MDA, the greater the chance that resistance will emerge against the medicines used."

Some people have argued that the unique, unprecedented threat posed by artemisinin resistance to global malaria control creates a special case for MDA. As ACTs are the only effective, practical treatment for malaria in most endemic zones, it is critical to retain their efficacy. With no other class of antimalarial drug likely to be ready in the next 5–10 years (Wells & Poll, 2010), the loss of artemisinins to parasite resistance would probably lead to sharp increases in morbidity and mortality due to malaria.

2. Limitations of existing interventions

2.1 DIAGNOSTIC TOOLS

An ideal diagnostic test is sensitive, rapid, field-ready and minimally invasive. The sensitivity of a diagnostic test depends on the intrinsic technical characteristics of the method, the quality and use of the test and the characteristics of the parasite and host population. Most published trials have shown that malaria rapid diagnostic tests (antigen-detecting, lateral flow tests) and field microscopy are similarly sensitive in the field (Ochola et al., 2006). Both methods, with adequate quality assurance, are sufficiently sensitive for field diagnosis of most symptomatic malaria infections. Rapid diagnostic tests are field-ready and fast, but they are not sensitive enough to detect low levels of parasitaemia as is often found in asymptomatic carriers. In population surveys, neither rapid diagnostic tests nor microscopy detects low parasite densities in asymptomatic individuals in low-transmission areas. Only an expert microscopist with adequate time will be able to detect lower parasite densities than most rapid tests (i.e. asymptomatic infections). Expert microscopy also has the advantage of quantification of parasite density and better species identification.

Nucleic acid detection tests (usually PCR) are increasingly considered the gold standard for diagnosing malaria in patients who are asymptomatic or who have a very low parasite density. PCR can detect parasite densities below the threshold of microscopy and rapid diagnostic tests; however, this method also has its limitations. Thus, the threshold of detection of the most sensitive PCR technique depends on the initial volume of blood from which the sample is extracted and on the technique used. Consequently, unless a relatively large volume of blood is taken, a person may have thousands of parasites and still test negative for malaria by PCR (Snounou & Singh, 2002). PCR also requires resources that are usually available only in reference laboratories, including sophisticated laboratory equipment, expensive reagents and technical expertise. When analyses are conducted outside a study area, the results are usually not immediately available, increasing the likelihood of patient loss to follow-up.

In addition to false-negative results due to poor sensitivity, false-positive results can be seen with all diagnostic techniques. False-positive results in microscopy are commonly due to artefacts. In the case of rapid diagnostic tests, false-positive results may be due to persistence of the histidine-rich protein 2 antigen. In PCR analyses, false-positive results may be due to sample contamination. False-positive results lead to misclassification and subsequent administration of treatment to people who do not have malaria. Neither rapid diagnostic tests nor PCR can generally distinguish between an asexual infection and gametocytaemia, which has important implications for the choice of treatment regimen, particularly in settings where the aim is to reduce transmission or eliminate malaria.

As the goal of containment and elimination is to provide antimalarial treatment to everyone harbouring parasites, the limitations of the diagnostic tools described above are a concern in areas where artemisinin resistance has emerged and where there are many asymptomatic cases. Even with the most sen-

sitive diagnostic testing of blood (e.g. with PCR), the true prevalence is still likely to be underestimated. Furthermore, all diagnostic methods are limited, in that malaria parasites spend a significant part of their life cycle in the human liver and in mosquitoes. While this is not likely to be a major cause of false-negative results, parasites resident in the liver will escape detection by even the most sensitive diagnostic blood test.

More research is needed to understand fully the characteristics of the asymptomatic population. The true proportion of people who are harbouring parasites at levels below the PCR detection threshold remains unknown. A survey with large-volume blood samples would help in making an estimate. Longitudinal studies of asymptomatic carriers would help to clarify the duration of infection, progression of their symptoms and their infectivity to anophelines. It is likely that many infected (asymptomatic) people eventually become symptomatic (Mutabingwa et al., 2001). In addition, long-term carriage of gametocytes before diagnosis is likely to increase transmission.

2.2 OBSERVATIONS IN AREAS OF ARTEMISININ RESISTANCE

Malaria surveys, focused screening and treatment and mass screening and treatment were conducted in Cambodia as part of national surveillance of malaria programmes and the operational research component of the artemisinin resistance containment project. These activities, consistent with previously published evidence, demonstrated the greater sensitivity of PCR than rapid diagnostic tests and microscopy in this low-transmission area. The results also showed that a high proportion of the people representing the potential 'infectious reservoir' of artemisinin resistance would not have adequate levels of parasites in their blood to be detected at the time of screening if only field microscopy and rapid diagnostic tests were used. While PCR has clear advantages from the point of view of sensitivity, the logistical difficulties of PCR testing currently make this method impractical.

Cambodia malaria surveys, 2007 and 2009

In the survey conducted by the Cambodia National Center for Parasitology, Entomology and Malaria Control in October 2007, 2.5 times more positives were detected by PCR than by microscopy (F. Ariey, personal communication, 2010). If PCR is considered the diagnostic gold standard in this context, the sensitivity and specificity of microscopy were 38% and 99.9%, respectively. An additional 332 infections missed by microscopy were detected by PCR, representing 62% of the 538 positive cases. This finding indicates that a high proportion of infections are below the limit of detection by microscopy.

These results are consistent with those of the containment survey in late 2009, when slides and blood spots were collected from 5795 people in Cambodia. Blood smears (n = 5340) were analysed by trained microscopists, and dried blood spots (n = 5346) were analysed by PCR. The prevalence of malaria as determined by PCR was approximately twofold higher than that ascertained by microscopy (D. Ménard, personal communication, 2010). The increase in detection threshold with PCR was higher for *P. falciparum* than for *P. vivax* infections. Of the 5346 samples analysed by PCR, 54 (1%) tested positive for *P. falciparum*.

These studies demonstrate the discrepancies between PCR and microscopy in this region. Research conducted in the Cambodia–Thailand border area showed that most people harbouring parasites in the blood had densities too low to be detected by rapid diagnostic tests or field microscopy. The tendency to misclassify positive cases as negative increases the likelihood that the drug-resistant phenotype will spread.

Mass screening and treatment, pilot study, Pailin

In November 2008, a mass screening and treatment feasibility study was conducted in the district of Pailin, as part of the operational research component of the artemisinin resistance containment project. The objective of the study was to identify the best methods for mass screening and treatment and to ascertain its effectiveness for eliminating artemisinin resistance. PCR analyses were conducted by the Institut Pasteur du Cambodge in Phnom Penh. New methods were explored to assess whether the necessary throughput, accuracy and speed could be achieved to scale up use of PCR.

The study showed that mass screening and treatment was impractical and unsustainable in this setting. In particular, high population mobility rapidly resulted in an outdated census and registration of residents. It was also anticipated that the campaign-style operation would have to be sustained for several years, and the necessary financial resources could not be guaranteed. The main reason for discontinuing mass screening and treatment was the complexity of the logistics. The project was considered to be extremely demanding in terms of human resources. For example, the screening exercise took approximately one week per village, whereas the zone of highest priority in western Cambodia contains several hundred villages. To obtain data from all the villages, either a single team would have had to work for several years or several dozen teams would have had to work for several months. Neither option was considered viable for providing information for the containment and elimination activities.

Focused screening and treatment, Pailin

Focused screening and treatment was considered to be more feasible than mass screening and treatment, since they can be applied to a smaller population. Focused screening and treatment was conducted in May 2009 and May 2010 in 20 villages in Pailin province (zone 1 of the artemisinin resistance containment project). Ten of the targeted villages had the highest outpatient prevalence of malaria in 2009 (72% of Pailin's *P. falciparum* cases). Blood spots were collected on filter papers during parasitological and demographic surveys in the study village, and PCR analyses were performed at the Institut Pasteur in Phnom Penh, a 5-h drive from the village. The distance between the village and the laboratory meant that an average of 11 days elapsed before the results of the screening tests were available. The delay resulted in loss to follow-up of a small number of patients (3/60).

2.3 IMPLICATIONS FOR MASS DRUG ADMINISTRATION

The artemisinin resistance containment project has made significant progress in reducing the detectable parasite prevalence in western Cambodia. Given the limitations of the currently available diagnostic tools, however, continuation of the same approaches will not necessarily lead to zero prevalence. The last surviving parasites may be present in people who have failed treatment and therefore carry the resistant phenotype. Elimination of the final parasites will require distinctly different tools.

Despite the problems that preclude systematic use of MDA in malaria control, the limitations in diagnostic testing described above indicate that its application in these circumstances might be prudent and beneficial. MDA would alleviate the effort and expenses associated with diagnostic testing as well as the problems associated with misclassification. For these reasons, MDA is considered by some people to be the only possible method for achieving elimination of artemisinin-resistant parasites.

3. Mathematical models of mass drug administration

A recent analysis of an MDA trial in western Cambodia was based on a model of the relative roles of MDA and increased coverage with presumptive treatment of clinical malaria (Song et al., 2010). The authors concluded that MDA combined with sustained high coverage with presumptive treatment of clinical malaria with ACTs could result in local elimination in western Cambodia. MDA markedly reduces the prevalence of all malaria infections, and, if the drug has a sufficiently long half-life, it will have a prophylactic effect at population level, temporarily reducing the basic reproduction number by rendering a large proportion of the population refractory to infection. Mathematical modelling showed, however, that a single round of MDA in western Cambodia will not reduce transmission permanently and the prevalence will return rapidly to pre-intervention levels.

At very high levels of transmission, a considerable proportion originates from asymptomatic, untreated individuals. Therefore, there is considerable redundancy in the transmission reservoir, and, as a consequence, presumptive treatment of all clinical malaria has relatively little effect on the incidence of disease. At lower levels of transmission, presumptive treatment of all symptomatic cases of malaria has a greater effect, depending on the proportion of transmission that derives from these individuals and the extent to which treatment reduces transmissibility. An incremental reduction in transmission (and consequently disease) will in turn eventually reduce the level of immunity in the population. This reduction in herd immunity will increase the proportion of all infections that are symptomatic. The time course and magnitude of these effects are uncertain. Transmission reduction is expedited by MDA in proportion to the coverage achieved, because MDA reaches all potentially transmissible infections.

MDA is likely to have a greater impact than mass screening and treatment for two reasons. First, owing to the limitations of current malaria diagnostic tests and the high proportion of asymptomatic individuals (see section 2.2), the proportion of infected people treated will be higher with MDA than with mass screening and treatment. Secondly, if the drug used in MDA has a reasonably long half-life, uninfected people will receive prophylaxis, significantly reducing their susceptibility to infection. In an area of seasonal transmission, use of MDA at the time of lowest infection prevalence (at the end of the dry season) could prevent the annual epidemic, as most of the population would be protected from infection.

4. Practical considerations for mass drug administration

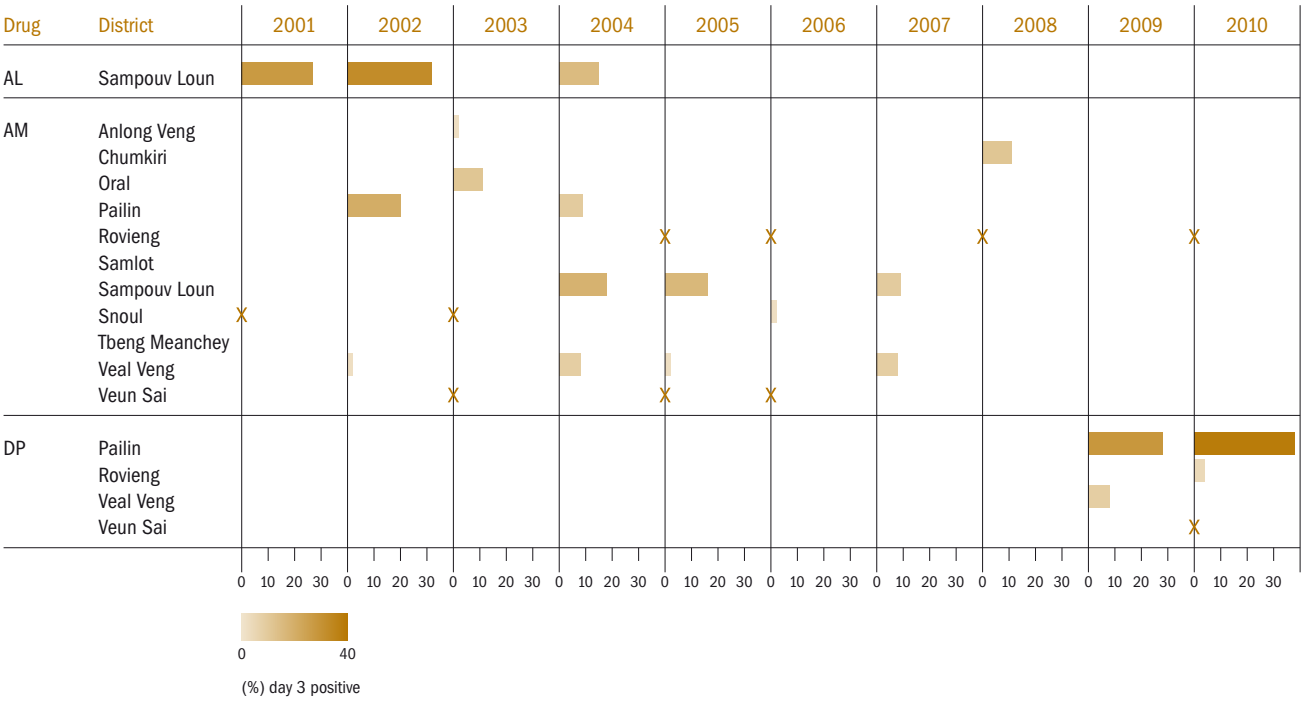
4.1 TARGET AREAS

Implementation of MDA requires a clearly defined target population. Unlike conventional MDA, in which the targeted zones are generally characterized by high parasite prevalence, the target area in the Greater Mekong subregion has a very low prevalence of parasites, which have a relatively high frequency of the artemisinin-resistant phenotype. The target areas of the artemisinin-resistance containment project were defined in 2008 on the basis of findings from studies of therapeutic efficacy conducted in sentinel sites, and some research data. The zones used for the artemisinin resistance containment project might not, however, be appropriate for MDA.

More research is needed before the precise target area for MDA can be delineated. The results of studies conducted between 2000 and 2010 in Cambodia, by district and type of treatment are presented in Figure 1, which shows the proportion of patients with *P. falciparum* parasitaemia on day 3, and in Figure 2, which shows the treatment failure rates on day 28. Figure 1 confirms clearly the presence of the artemisinin-resistant phenotype in western Cambodia (Pailin) in 2009–2010. Modelling conducted by the Mahidol Oxford Research Unit in 2009 suggested that artemisinin resistance would be unlikely if the proportion of patients with a positive smear on day 3 was less than 3% (Stepniewska et al., 2010). This threshold was further extended to include sites at which the proportion of patients who were parasitaemic on day 3 is 3–10%, considered to be in a grey zone, in which caution and increased scrutiny are required. Further, if ≥ 10% of patients are found to be parasitaemic on day 3, studies should be initiated with oral artesunate monotherapy to investigate artemisinin resistance (WHO, 2010a). These are working thresholds and additional data are needed to refine them. Without this critical information, it will remain difficult to define where it would be best to apply MDA.

Methods for defining target areas are needed quickly, given the urgency of containing or eliminating artemisinin resistance. The GPARC recommends intensified surveillance of the efficacy of artesunate in areas bordering those with a confirmed risk of resistance (i.e. ≥ 10% of patients positive on day 3) (WHO, 2011). Data from surveillance studies could be used to produce geo-statistical maps, showing areas of risk based on parasite prevalence, population density and the prevalence of the main vectors. Once the target area is identified, it will be possible to examine the feasibility and safety of conducting MDA, given the available resources. The identification and validation of molecular markers of artemisinin resistance would vastly improve the resolution of these maps.

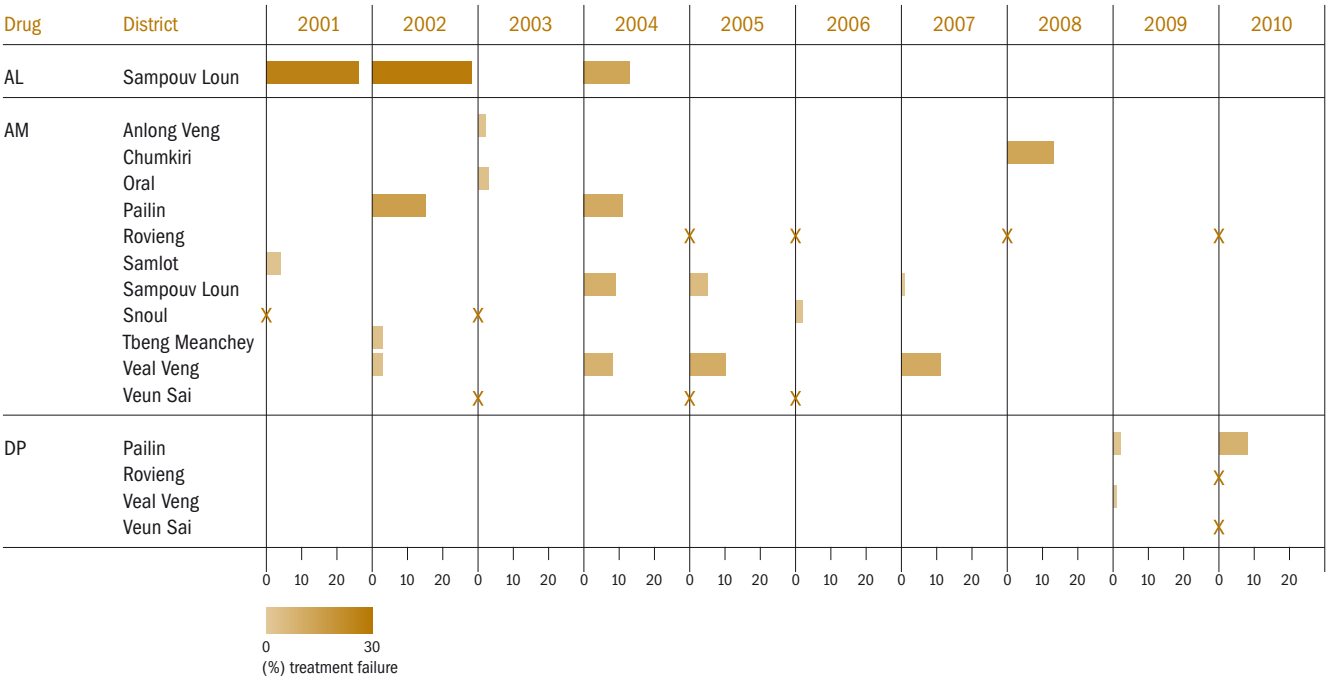
FIGURE 1. Percentages of patients with *Plasmodium falciparum* parasites on day 3 after treatment with an ACT during therapeutic efficacy studies and clinical trials conducted in Cambodia, 2001–2010



AL, artemether–lumefantrine; AM, artesunate–mefloquine; DP, dihydroartemisinin–piperaquine

X indicates that a study was conducted and the result was 0%.

FIGURE 2. Percentages of patients with treatment failure on day 28 after treatment with an ACT during therapeutic efficacy studies and clinical trials conducted in Cambodia, 2001–2010



AL, artemether–lumefantrine; AM, artesunate–mefloquine; DP, dihydroartemisinin–piperaquine

X indicates that a study was conducted and the result was 0%.

4.2 TARGET PERIOD

The participants also discussed the timing of MDA. The Chinese used a 'spring treatment' against the relapse of vivax malaria (Qing, 2000; von Seidlein & Greenwood, 2003). The authorities identified areas that had had relatively high case loads during the previous summer and inferred that a high proportion of people resident in those areas would be at risk for relapse during the coming summer. In this method, latent hypnozoites were targeted before they had the opportunity to mature and result in further transmission.

In contrast to conventional MDA, which is usually implemented during periods of high parasite prevalence, MDA for elimination should be done during the low-transmission season, when the prevalence of parasites and the numbers of mosquitoes are at their lowest. This departure from conventional MDA mitigates the risk for selecting for resistance, as a smaller parasite biomass lowers the probability of encountering a resistant mutant, and there will be a seasonal reduction in anophelines that may acquire and then transmit resistant mutants. In the Greater Mekong subregion, the appropriate period would be the second half of the dry season, i.e. March, April and May. The frequency of administration within this window will depend on the drug selected.

4.3 CHOICE OF DRUG

The participants considered the safety, tolerability, convenience and probable efficacy of several drugs against artemisinin-resistant *P. falciparum* that might be used in MDA.

Artemisinin-based combination therapies

Mathematical models of MDA indicate that, when elimination is the target, the best treatment is one that leads to the greatest reduction in transmissibility and provides the longest period of prophylaxis (thus preventing acquisition of infection). The 'last man standing' model predicts that if artemisinin resistance increases the transmission potential of a treated infection, artemisinin resistance will steadily increase during routine use of ACTs for the treatment of clinical malaria (Maude et al., 2009). When the model was used to simulate a single round of MDA with an ACT, it predicted only a slight increase in the spread of artemisinin resistance. Thus, the trade-off between the likelihood of success of MDA with a given drug (correlated directly with the efficacy of the drug) against the increased selection pressure incurred with that drug is predicted to be in favour of using the ACT, especially if the partner drug is eliminated slowly.

The group did not, however, endorse use of an ACT for MDA, because it was considered irrational to use an artemisinin-based treatment to kill artemisinin-resistant parasites. The decision also took into account the 'last man standing' model, which projects that ACTs will be more effective at targeting artemisinin-sensitive parasites, leading to an increase in the proportion of resistant infections as the parasite population decreases (Maude et al., 2009). Failure to remove all artemisinin-resistant parasites would allow them to re-populate.

Atovaquone–proguanil

The group considered the advantages of AP over the five ACTs recommended by WHO. AP has the same advantages of safety in the general population, efficacy, good manufacturing practice, commercial production, acceptability and tolerability (Boggild et al., 2007; Schlagenhauf et al., 2003; WHO, 2008b);

however, the primary advantage of AP over ACTs is that there is no known cross-resistance with artemisinin.

The obvious risk of using AP for MDA is selection for a completely atovaquone-resistant, stable genotype (Vaidya & Mather, 2000), which would compromise its use for chemoprophylaxis. AP is among the most widely recommended medicines for the prevention of falciparum malaria in travellers (Shanks, 2008). Before AP can be recommended for use in MDA, a complete and independent review of the available data, particularly for pregnant women, is needed. Although the data on the safety of this drug may be inadequate for total assurance about its use for such subpopulations, they suggest that the drug would be safe if used as MDA.

Primaquine

Primaquine was considered to be a necessary addition to the proposed MDA package, in order to block transmission of artemisinin-resistant parasites. Addition of primaquine does, however, raise safety concerns, as there is growing evidence that a single 45-mg gametocytocidal dose of primaquine can be harmful (Baird & Surjadjaja, 2011). In a study of primaquine co-administered with an artemisinin in the United Republic of Tanzania, decreased haemoglobin concentrations were observed in children given a single dose of primaquine, most markedly in those who were G6PD deficient (Shekalaghe et al., 2010). The authors did not recommend wide-scale administration of primaquine, even in areas with a relatively low prevalence of G6PD deficiency.

Primaquine has generally been used without prior screening for G6PD deficiency, an X-linked recessive hereditary disease characterized by abnormally low levels of G6PD, which predisposes people to haemolysis after exposure to a number of environmental factors and antimalarial drugs. Initial conclusions about the safety of primaquine were based largely on clinical trials undertaken in African Americans carrying the A-variant of the G6PD gene. The susceptibility to primaquine-induced haemolysis of people with this variant is low and self-limited; however, according to at least one expert, the 45-mg dose may not be safe for people with the variants of G6PD deficiency that occur in Asia and the Pacific (Clyde, 1981).

With the exception of three of the many dozens of known variants, little is known about how a given G6PD deficiency variant will respond to primaquine. In addition, the use of primaquine is contraindicated in pregnancy, because the G6PD deficiency status of the fetus cannot be assessed (Hill et al., 2006). If the safety of a gametocytocidal dose of primaquine could be demonstrated in women and children carrying the dominant G6PD deficiency variants in Cambodia and Thailand, this would increase the likelihood of safety for the fetuses of women who did not realize they were pregnant during a cycle of MDA and who were treated with primaquine.

Questions also remain about the lowest effective gametocytocidal dose of primaquine and the optimal schedule by which it should be given with AP. The results of research in Cambodia suggested that a dose as low as 9 mg administered with an ACT effectively prevented infection of mosquitoes (Song et al., 2010). The early clinical trials that established 45 mg as the minimal effective single dose were performed without a companion blood schizontocide (Rieckmann et al., 1968; Rieckmann et al., 1969).

The sensitivity of people with the dominant G6PD deficiency variants in Cambodia and Thailand to primaquine must be assessed before primaquine is administered on a large scale. It is possible that some blood schizontocides act synergistically with primaquine against gametocytes. This possibility and the optimal schedule of primaquine administration must be examined before the drug is administered with AP in MDA. A lower dose of primaquine would probably provide a larger margin of safety (Lawpoolsri et al., 2009).

Summary of drug choices

The evidence with regard to the most appropriate drug for MDA in Cambodia and Thailand is inadequate to allow a choice. A demonstration of the safety of an optimized schedule and dosage of primaquine combined with AP is a prerequisite for MDA. Addition of primaquine to AP would substantially increase the likelihood of achieving elimination by arresting transmission of gametocytes; however, the benefit of MDA in potentially eliminating artemisinin-resistant parasites must be weighed against the risk of losing AP as an effective treatment and chemoprophylaxis for residents and visitors to the areas in which MDA is conducted.

4.4 REACHING THE TARGET POPULATION

Two approaches to implementation of MDA were considered: (1) targeting small populations (i.e. villages), as new evidence of artemisinin-resistant parasites appears; and (2) targeting areas known to harbour the resistant strains as well as adjacent areas. Advocates of the second approach considered that piecemeal attacks on pockets of identified resistant parasites could be interminable and would be futile, as unidentified resistant strains would spread. Although the group tended towards the broader approach to MDA, most participants agreed that implementation could not begin until more evidence was available. First, the target area has yet to be defined; its surface area and population size both have implications for implementation. The expert panel also considered the logistics of mass drug distribution and monitoring compliance and adverse events. The indicators of success are also yet to be defined. The group therefore suggested to conduct a pilot MDA, so that evidence-based decisions could be taken on the operational framework for large-scale MDA.

In view of the special characteristics of the populations living on the Cambodia–Thailand border, it will be difficult to reach all of them. The prevalence of G6PD deficiency in the population might make this group vulnerable, given that primaquine would be administered. Achieving good coverage will also be complicated by the large number of migrants who pass through the target area (see section 5.2). A comprehensive study of the risks for these subgroups of the population is needed before mass implementation (see section 7.2).

4.5 FREQUENCY OF MASS DRUG ADMINISTRATION ROUNDS

Most of the experts agreed that several rounds of MDA will be required, as complete coverage during each round is unlikely (Bruce-Chwatt 1983; Garfield & Vermund 1983). In a mathematical model that included several malaria control parameters, MDA was characterized by one or more annual 3-month pulses with an ACT or AP during the low-transmission season (Maude et al., 2009). No consensus was reached at the meeting on the number of rounds required or their frequency.

The goal of subsequent rounds of MDA would be to reach people who were initially missed as well as those who were treated but who were subsequently reinfected from the parasite reservoir. In addition, blood schizontocides do not reach liver-stage parasites in recently infected people, and mosquitoes might have been feeding on infected people who escaped the initial dosing. The short plasma half-lives of AP and primaquine allow for greater flexibility in administration, so that they can be given at short intervals if necessary.

Modelling has shown that, if coverage with a single round of MDA is incomplete (i.e. some infections remain untreated) and no other intervention is applied, the prevalence of malaria in the population will rapidly return to pre-intervention levels. The rate at which it returns depends on the force of infection, which can be inferred from the pre-intervention prevalence. If the initial prevalence is sufficiently low or an additional sustained intervention (such as distribution of insecticide-treated nets or high coverage with treatment of presumptive clinical infections) is added, the prevalence will probably not return to pre-intervention levels within a given time (e.g. one year). Further rounds of MDA at regular intervals will thus result in an overall decrease in prevalence, approaching elimination.

4.6 PILOT PROJECT

The group members agreed that a pilot project was needed to guide successful large-scale MDA. The pilot study would allow testing and evaluation of the operational framework in a subsample of the target population (e.g. 100 000 people), before MDA was scaled up to the estimated several million people living in the target zone. A successful pilot project would give stakeholders the necessary evidence about MDA. It was acknowledged that this cautious, time-consuming approach might allow further spread of artemisinin resistance. Nonetheless, most participants considered that it would be unwise to proceed to a large-scale programme without more background information.

5. Criteria for successful mass drug administration

5.1 EFFECTIVE COMMUNICATION OF RISKS AND BENEFITS

MDA in Cambodia or Thailand will require leadership by the national malaria control programmes and broader political and community support. People who are unlikely to be carrying malaria will be asked to consume antimalarial treatment on more than one occasion. Therefore, a clear, comprehensive communication strategy will be required to allow potential participants to make informed decisions about their participation and that of their children. Distribution of any treatment on a large population scale carries inherent risks, as almost any treatment can have serious side-effects in a minority of people. The risk for adverse events should be quantified in terms of probability and severity on the basis of the best evidence available, communicated to all stakeholders and included in the ethical considerations for administering the drugs. The potential benefits of successful MDA, i.e. elimination of artemisinin-resistant falciparum malaria, must be emphasized, as these are likely to be the primary motivation for people considering participation in multiple rounds of MDA.

5.2 MOBILE AND MIGRANT POPULATIONS

Mobile and migrant populations are important factors in the spread of infectious diseases, including artemisinin-resistant parasites, both within countries and across borders (Roper et al., 2004). Migrant populations are dynamic, their length of stay depending on their reason for migrating. Establishing and maintaining communications with undocumented migrants who prefer to remain anonymous to the authorities is a challenge, but it is critical to consider how to target mobile and migrant populations in MDA.

Thailand has become the primary destination for irregular Cambodian labour migrants. For example, it is common for Cambodian migrants to leave for seasonal work on the Thai side of the border. There is also migration into Cambodia from Viet Nam and China. Migration from Cambodia and Thailand is mainly to Malaysia, the Gulf countries and the Republic of Korea; however, it is internal migration that may be the largest obstacle to MDA. According to a review of migrant populations conducted by the Malaria Consortium (2009), internal migrants within Cambodia make up 35% of the population; of these, 62% migrate within their own province and 37% outside their province. The migrants include traditional forest inhabitants, ethnic minorities, inhabitants of the forest fringe, temporary migrants, refugees, displaced persons and new forest settlers.

Achieving good coverage of these target groups will be a challenge for MDA. A study of 2889 migrant workers in 33 villages in Cambodia showed that migration was due mainly to seasonal labour on farms, and that most workers left their homes in either June or December. MDA between March and May, before departure of the migrants, might therefore result in relatively high coverage of mobile populations, although it will be difficult to ensure complete coverage. In studies of focused screening and treatment, population migration proved to be

a major limiting factor. Migrants returning from Thailand to Cambodia after MDA are unlikely to represent a threat to the project if they are importing sensitive parasites from beyond zone 1. One assumption of the MDA strategy is that the effect of the intervention will be temporary and that repopulation of the MDA zone by parasites from surrounding areas will almost certainly occur.

6. Potential challenges to mass drug administration in the context of artemisinin resistance in the Greater Mekong subregion

The potential problems associated with MDA, both hypothetical and concrete, were discussed in detail. The main arguments against MDA are listed below.

6.1 DISRUPTION OF CURRENT CONTAINMENT ACTIVITIES

Since 2008, Cambodian and Thai health officials and their global partners have been implementing measures to control malaria and contain or eliminate artemisinin-resistant parasites. These activities were supported by the Bill & Melinda Gates Foundation and will be expanded with Global Fund Round 9 (Cambodia) and Round 10 (Thailand) grants. In endemic areas of zone 1 in western Cambodia, containment included increasing the availability of reliable diagnosis and treatment through village malaria workers, establishing public–private sector partnerships to improve care in the private sector, enforcing a ban on artemisinin monotherapy, providing enough long-lasting insecticidal nets to cover every resident and supplying at least one insecticide-treated hammock net per household. In addition, a village-by-village focused screening and treatment programme was implemented in 20 endemic zone 1 villages in Pailin, western Cambodia. Some experts at the meeting expressed the view that these efforts, diligently applied, would ultimately lead to containment or elimination of the artemisinin-resistant phenotype and that imposing MDA as an element of the strategy might inadvertently threaten the success of these more conventional operations.

6.2 EMERGENCE OF ARTEMISININ RESISTANCE ELSEWHERE

The clearest evidence of delayed clearance times after treatment with ACTs comes from western Cambodia and neighbouring Thailand. Routine efficacy trials in the Greater Mekong subregion (Myanmar–Thailand border, China–Myanmar border and one province in Viet Nam) have shown, however, increased proportions of patients who are still positive on day 3 after ACT. The presence of artemisinin resistance is still being confirmed. While there is no indication of prolonged clearance times with artemisinin monotherapy or ACT outside the Greater Mekong subregion, using MDA to contain or eliminate transmission of resistant *P. falciparum* in multiple foci simultaneously would be far more logistically challenging than addressing the issue in Cambodia and Thailand alone. The search for additional foci of delayed clearance and treatment failure should be intensified by routine follow-up of malaria cases confirmed at health facilities and routine therapeutic efficacy studies conducted across as wide a region as possible.

6.3 ACHIEVING THE NECESSARY HIGH RATES OF COVERAGE

Much of the transmission of malaria and the resulting morbidity and mortality in Thailand and western Cambodia are associated with

mobile and migrant populations and individuals who visit forested areas. These groups are frequently missed by teams that conduct focused screening and treatment, parasitaemia surveys and other community-based activities; population coverage with focused screening and treatment is only 70%. The expert panel expressed concern that the people most likely to be missed would also be those at greatest risk of carrying malaria parasites. In addition, the MDA programme would require that nearly all individuals take at least daily doses of medication (most likely multiple tablets) for three days. While adherence to three-day regimens has been encouragingly high in the sites of pilot focused screening and treatment, it is not clear whether asymptomatic people would be motivated to complete the course of medication without a diagnosis. Direct observation to ensure that all doses of a drug are taken would require an enormous workforce, and coverage would probably be lower than that in focused screening and treatment for the relatively small number of people who tested positive.

6.4 POTENTIAL SELECTION FOR RESISTANCE

Use of any antimalarial drug for the treatment of symptomatic or asymptomatic malaria incurs the risk of selecting for minority or rare resistant strains. Although the expert panel uniformly proposed AP as a potentially safe drug for MDA in the face of artemisinin-resistant parasites, the serious problem of resistance to this drug combination was raised. Mechanisms of resistance to both atovaquone and proguanil have been described and appear to be relatively easily induced when either compound is used alone. The resistant mutants are completely resistant, viable and stable (Vaidya & Mather, 2000). Use of these drugs in a fixed-dose combination, under direct observation and for low-density asymptomatic infections, as in MDA, would minimize this potential risk but not eliminate it. As molecular markers for atovaquone and proguanil resistance have been described, it should be possible to monitor them during routine treatment in the months and years after MDA. Time- and geographically-limited MDA would result in less risk for resistance than indefinite or unregulated therapeutic use. Moreover, resistance to atovaquone, if it did emerge, would not be expected to confer cross-resistance to currently recommended first- or second-line treatments. Some participants, however, emphasized the importance of preserving AP as one of the few non-artemisinin-based regimens for treating or preventing multi-drug-resistant malaria. At the least, use of this product would require careful consultation with the manufacturer.

6.5 ETHICAL ISSUES

The ethical issues associated with administering antimalarial agents presumptively to an entire population in which most people are not infected must be considered carefully. Atovaquone and proguanil both have good safety profiles as monotherapies and in combination. At treatment doses, the combination has been associated with infrequent mild gastrointestinal symptoms, headache and transient increases in transaminase levels. Very few case reports of severe adverse reactions associated with AP have been published. As a prophylactic regimen, it is widely used and generally well tolerated. An independent review of preclinical data and in post-marketing surveillance have not suggested any reproductive

toxicity. Taken alone, however, AP may not reduce the infectiousness of human malaria carriers to mosquitoes, and use of primaquine is thus indicated.

In people with G6PD deficiency, primaquine may induce mild-to-severe acute intravascular haemolysis. Although the prevalence of G6PD deficiency has been measured at a relatively high 15% in the areas in which MDA might be used, no information is available to forecast the clinical consequences of primaquine challenge in the population along the Cambodia–Thailand border. It might be unethical to administer primaquine to reduce malaria transmission in the absence of certainty about its safety, especially in the context of MDA (Baird & Surjadjaja, 2011).

6.6 EVIDENCE BASE FOR A RATIONAL MASS DRUG ADMINISTRATION STRATEGY

Some participants raised concerns about the inherent limitations of surveillance data on both sides of the Cambodia–Thailand border and about poor coordination between the two countries of the available surveillance intelligence. These limitations make it difficult to define a target area for MDA that would cover all resistant parasites. Only recently have efforts like focused screening and treatment and expanded networks of village malaria workers begun to provide detailed information about the geospatial distribution of malaria infection and illness. Rational MDA, i.e. a plan with some evidence-based chance of achieving its aims, will require drawing the geographical bounds of implementation on the basis of the known distribution of resistant phenotypes. The current data are not sufficient for this.

7. Consensus statement

The consensus of the meeting was that MDA should be considered as a potential component of the integrated strategy initiated in western Cambodia and eastern Thailand to contain and, if possible, eliminate artemisinin resistance. Unless artemisinin-resistant parasites are rapidly eliminated, the risk that they will spread within and outside the region remains high; this would have potentially catastrophic consequences for global malaria control. Ongoing containment activities have been associated with a reduction in incidence but have not eliminated resistant *P. falciparum* parasites in the area. MDA with effective drugs would, in principle, bring about a further significant reduction in the parasite biomass (including resistant parasites) and, when combined with other appropriate interventions, would probably greatly diminish the probability that the resistant phenotype could escape. Nevertheless, most participants agreed that MDA would probably not permanently interrupt transmission of *P. falciparum* in the area.

There was broad agreement that there is insufficient evidence to mount a rational, safe, large-scale MDA operation covering all areas likely to harbour the artemisinin-resistant phenotype. First, the geographical limits of the resistant phenotype are not clearly defined. Secondly, although the participants agreed in principle that primaquine should be included as a gametocytocidal medicine in any MDA operation, evidence of its safety in people with Cambodian or Thai G6PD deficiency variants is inadequate. Furthermore, information is lacking about optimizing co-administration of primaquine with AP, which is considered to be the most appropriate drug for MDA in this context. Finally, strategies for achieving high coverage with MDA – an extremely important determinant of its potential impact, especially with respect to social, demographic and logistical factors – are as yet poorly developed, as are broader indicators of the success or failure of a large-scale MDA operation.

Therefore, the majority opinion was to consider a pilot MDA operation in the dry season in early 2012, of sufficient scope to allow scaling up for possible broader operations. Lessons learnt from the pilot study would be used to base decisions about a strategy for a broader MDA operation, should experience indicate that expansion would be appropriate. Nevertheless, a pilot study cannot address all the issues raised.

A pilot MDA operation will offer the opportunity to reduce the resistant parasite reservoir in the area rapidly, while simultaneously strengthening the evidence base and experience with MDA. It will also provide an opportunity for gathering essential evidence on the safety and efficacy of MDA regimens. Although the time lost by conducting a confined pilot MDA introduces a real risk to achieving the goal of containment and elimination, evidence on which to base a rational, more extensive MDA operation was considered to be insufficient; if such an operation was attempted, the MDA option might be lost altogether. The potential importance of MDA extends beyond the aims of the artemisinin resistance containment project and into the broader realm of global malaria elimination strategies.

In summary, the majority opinion was for use of MDA for containing artemisinin-resistant parasites in the Greater Mekong subregion but only after evidence has been obtained to address the critical questions. To this end, the group recommended immediate planning of a pilot MDA operation in western Cambodia or eastern Thailand and the collection of essential information on the safety and efficacy of the candidate drugs for MDA.

7.1 RECOMMENDATIONS

- Immediately plan and seek funding for a pilot MDA operation, and use this operation to obtain the necessary training, experience and evidence for rational design of any subsequent MDA operations on almost any scale;
- Immediately plan and seek funding to determine the safety of a gametocytocidal dose of primaquine in people with known G6PD deficiency variants in Cambodia and Thailand;
- Immediately plan and seek funding to identify the minimally effective and gametocytocidal dose of primaquine and the optimal schedule for administering it with atovaquone and proguanil;
- Immediately conduct additional studies of therapeutic efficacy to better define the geographical reach of artemisinin-resistant parasites, with a focus on the Myanmar–Thailand border.

7.2 RESEARCH PRIORITIES

Demonstrate the safety of the gametocytocidal dose of primaquine in carriers of the dominant variants of G6PD deficiency in Cambodia

Assurance of the safety of a gametocytocidal dose of primaquine among Cambodians with G6PD deficiency is an absolute requirement for any MDA programme that includes primaquine (MDA without primaquine might be considered reckless). If a gametocytocidal dose of primaquine is proven to be potentially unsafe in this population, a point-of-care diagnostic test for G6PD deficiency would be required in an MDA regimen that included primaquine. An escalating dose challenge in healthy adult volunteers with G6PD deficiency representing the dominant G6PD variants in Cambodia would be a logical starting-point, followed by testing of safe doses in patients with acute malaria.

Optimize the dose and treatment schedule of primaquine when used as a gametocytocide in combination with AP treatment

Use of primaquine as a gametocytocide should be evaluated at varying doses and schedules in combination with AP. Ideally, laboratory-reared anophelines would be fed directly on gametocytaemic human volunteers given different single doses of primaquine, as might be used in an MDA treatment regimen. For example, doses of 10, 15, 30 and 45 mg primaquine administered as a single dose on day 0, 1, 2 or 3 (or two doses, should these prove ineffective or less than ideal) could be tested.

Gather and assess all available data on the safety of AP in pregnant women

Mass administration of AP would highly probably expose fetuses to these drugs early in development, i.e. before the mother knew that she was pregnant. The risk of this exposure to both the fetus and the mother must be evaluated on the basis of the best, most complete collection of new data available.

Design protocols for optimally defining the geographical bounds of the area of MDA, and intensify the gathering of information for the protocols

The geographical bounds of any area in which MDA is conducted must be based on rational, consistent weighing of the essential evidence. Research is required to define the evidence and its use in drawing the physical, social and demographic boundaries of an area for MDA.

Develop a set of indicators of the success of MDA

MDA has not previously been used to eliminate a specific phenotype of *Plasmodium*, and no standardized means of assessing success or failure have been developed. This will require forethought, planning, review and validation of metrics.

Develop tools for surveillance of compliance and serious adverse events in connection with MDA

Although these tools might be used to measure success, they require real-time monitoring and decision-making to ensure the safety of the population receiving MDA and to maximize the probability of success. For example, a data and safety monitoring board should review reports of serious adverse events and make recommendations to the authorities responsible for the MDA programme.

Validate point-of-care diagnostics for G6PD deficiency

The inclusion of gametocytocidal therapy in MDA may require screening for G6PD deficiency before administering primaquine to large numbers of people, most of whom may not be infected. The availability of a simple, inexpensive, reliable point-of-care diagnostic test would make such use of primaquine safe and practical, whereas today it is not.

Prepare protocols and checklists for 'socializing' MDA

Populations being considered for MDA should be surveyed to gauge their attitudes and to help design information campaigns before MDA. Community leaders must be consulted on issues like maximizing coverage and understanding migrations and other substantial movements of people, such as pilgrimages and holidays.

Better understand the epidemiology of hypo-endemic malaria

A series of studies is needed in this area. Surveys of prevalence with PCR diagnosis in larger volumes of blood and repeated testing on consecutive days would help define the sensitivity of PCR with conventional blood sampling. This information could also be used in studies of mosquito infectivity at the levels of parasitaemia typical in affected communities. Longitudinal studies to determine the durability of the asymptomatic carrier state would permit better understanding of the infection and transmission dynamics in these communities.

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