Minutes of the Drug Resistance and Containment Technical Expert Group (TEG)

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Abbreviations

ACT    artemisinin-based combination therapy
ARC3   artemisinin resistance confirmation characterization and containment
APLMA  Asia-Pacific Leaders Malaria Alliance
AusAID Australian Government Overseas Aid Program
BMGF   Bill & Melinda Gates Foundation
DFID   Department for International Development
DP     dihydroartemisinin-piperaquine
ERAR   Emergency response artemisinin resistance
GMS    Greater Mekong subregion
GWAS   genome-wide association studies
K      parasite clearance rate constant
MDA    mass drug administration
MMV    Medicines for Malaria Venture
MPAC   malaria policy advisory committee
MFLT   multiple first-line treatments
PC     parasite clearance
PCR    polymerase chain reaction
RSC    regional steering committee
RAI    Regional Artemisinin Resistance Initiative
SNP    single nucleotide polymorphism
SLH    slope half-life
TEG    technical expert group
TES    therapeutic efficacy studies
TRAC   Tracking Resistance to Artemisinins Collaboration
USAID  United States Agency for International Development
WWARN  Worldwide Antimalarial Resistance Network
WHO    World Health Organization
Summary and recommendations

Is there evidence for the emergence of artemisinin resistance in South America?

Based on review of the data from Suriname and Guyana showing a substantially increased proportion of day 3 positive patients after treatment with artemether-lumefantrine, compared to previous data, the TEG considered this a region of suspected artemisinin resistance (following the WHO working definition). The malaria policy advisory committee (MPAC) at its meeting of March 2013 did not consider these findings as definite evidence of artemisinin resistance, and decided that a designation as tier I was not justified. The TEG, at its current meeting, endorsed the proposal to conduct detailed confirmatory studies in Suriname and Guyana and encouraged bordering countries, such as French Guyana, to conduct therapeutic efficacy studies (TES) strictly following the WHO protocol 2009. The TEG also recommended strengthening the malaria control measures in these countries.

Results of the TRAC study

The detailed TRAC study has confirmed areas in South East Asia where slow clearance phenotype \( P. falciparum \) had been identified earlier by high day 3 positivity rates during routine TES and has also identified new areas where increased vigilance is needed. Comparison of the detailed parasite clearance data from the TRAC studies with that of day 3 positivity rates during TES, supplemented by preliminary modeling results, indicates that the current threshold of \( \geq 10\% \) day 3 positivity rate for defining suspected artemisinin resistance is appropriate. Therefore, the TEG recommendations from the meeting in 2012 on day 3 threshold and confirmatory efficacy studies were not amended. The TEG recommended replacing the current first-line treatment, atovaquone-proguanil for uncomplicated falciparum malaria in Western Cambodia since atovaquone-proguanil is like a monotherapy, vulnerable to resistance. The best option seems the fixed combination of pyronaridine-artesunate, but a study must be conducted urgently to confirm its efficacy in Western Cambodia. The extension of ACT regimens (dihydroartemisinin-piperaquine or artemether-lumefantrine) from 3 to 5 or 7 days, could be an alternative option in areas where ACTs are failing, but this will also require additional efficacy and safety studies. The TEG recommended that modeling studies on piperaquine pharmacokinetics using extended courses of the ACT should be conducted to complement the clinical studies.

Recent developments on assessing parasite clearance

Characterization of the parasite clearance curve is considered as an important tool for measuring the therapeutic response to artemisinins. The tool developed by Worldwide Artemisinin Resistance Network (WWARN) requires the identification of the log-linear part of the parasite clearance curve and from this assesses the parasite clearance half-life. At the request of WHO, an alternative tool has been developed using an Excel®-based application, which takes into account the initial ‘lag phase’ and the terminal ‘tail phase’ of the clearance curve. These phases may represent important biological processes, but their roles in defining artemisinin resistance remain to be shown in parasite heritability studies in low transmission areas. It was agreed that the new tool would be tested by C. Plowe using the data from the Artemisinin Resistance Confirmation Characterization and Containment (ARC3) project.

Update on molecular markers for artemisinin resistance

Although much progress has been made over the last year, and regions in the parasite genome strongly correlating with delayed parasite clearance phenotype have been identified, a molecular marker for artemisinin resistance is not yet available. The prediction is that in the near future a set of region-specific single nucleotide polymorphisms (SNPs) will be able to identify artemisinin resistant \( P. falciparum \) with adequate specificity and sensitivity. This would obviously provide an excellent tool to monitor the spread of artemisinin resistance in the region. However, there are probably multiple SNPs involved (e.g. a mosaic of mutations associated with the phenotype that vary among parasite
populations). The molecular analyses required for genotyping will likely be of high sophistication. The TEG can facilitate these by soliciting the help of centers of genomic research. The TEG further recommended that additional sources of parasites (e.g. filter paper blood spots and if possible blood depleted of white blood cells) should be sampled on a more routine basis during TES and research trials, which could then be used to do the molecular analyses of resistance genes and parasite gene flow.

**Update on in vitro artemisinin susceptibility testing**

Several in vitro methods for assessing artemisinin susceptibility are available for research purposes but there is no test available yet, which can be recommended as standard method. However, tests focusing on inhibition of ring stage development, as well as the use of short term (4-6 hours) exposure to artemisinins appear to have the best sensitivity to identify the resistant in vivo phenotype. In addition multi-pulsing and 6-day (minimum) recovery assays are showing promise.

**Multiple first-line treatments: outcome of recent modeling efforts**

Implementation of multiple first-line treatments (MFLT) has been suggested as a strategy to reduce the risk of emergence and spread of artemisinin resistance. The TEG discussed two mathematical models which yielded divergent results on the benefit of MFLT in certain settings, so that a general recommendation on the implementation of MFLT could not be given at this time. However the concept warrants further investment in research and modeling efforts, and the TEG recommended that the different modeling groups collaborate to understand the reasons for these differences. The benefits expected by MFLT should be well defined and these will vary depending on the settings. In future work, it will be important to address the problem of resistance to partner drugs as well. If resistance to artemisinins exists, it is more likely that resistance to partner drugs will also develop, and vice versa. Consequently, resistance to ACT partner drugs is also an important concern and needs to be taken into consideration. It was noted that MFLT is already a reality in some places, for example because different donors support the distribution of different drugs and, for this reason, a sequential deployment strategy may be difficult to implement in these countries. Other approaches delaying resistance, such as triple combinations (three different chemotherapeutic principles in a single therapy) should also be considered.

**Emergency response to artemisinin resistance in the Greater Mekong subregion**

The TEG discussed the ERAR, and recognized this as a framework for action, and thus not an action plan detailing and prioritizing interventions for implementation. Since containment efforts in regions with artemisinin resistance embrace elimination of falciparum malaria where it is feasible, the problem of asymptomatic carriers should also be addressed, which requires detection methods with adequate sensitivity. Regarding updating the tier designation and maps, the TEG will make recommendations but it recognized that the final decision is the responsibility of the national malaria programmes. Tier designation can be assigned based on: studies assessing day 3 positivity rates, and/or results of more detailed research studies in the place where artemisinin resistant parasite infection is suspected to have been acquired. In specific areas it can be important to recognize the area of origin of the malaria infection in order to designate a tier zone, for instance patients traveling cross border for their health care. The TEG discussed the current tier designation and recommended, based on recent study results that the following additional provinces should be designated as tier I: Bago East and Kayin provinces (Myanmar); Preah Vihear province (Cambodia). Kayah (Myanmar) is likely to meet the tier I designation but the recommendation is pending the availability of quality control of data from the TES. The district of Attapeu in Lao PDR, currently designated as tier II, may be changed to tier I after review of new data. Changing tier designation will of course have implications for the Regional Artemisinin Resistance Initiative (RAI, see below). Maps will be prepared for the RAI; these will be released into the public domain after discussion with national malaria control programmes.
Update on the recent call from the Global Fund on artemisinin resistance

The TEG was updated on the recently established RAI of the Global Fund. The RAI was built on the ERAR. With this initiative approximately 100 million US$ will be allocated specifically for the regional containment of artemisinin resistance with activities in Cambodia, Myanmar, Thailand, Viet Nam, and Lao PDR. The TEG welcomed this additional funding for artemisinin resistance from the Global Fund. The overall aim is elimination of *P. falciparum* in areas of artemisinin resistance. The TEG reiterated that while the ultimate goal of containment efforts remains the elimination of falciparum malaria in areas with resistant parasites, the epidemiological realities in some countries such as Myanmar are such that interim objectives shall be containment of artemisinin resistant falciparum malaria, which is understood as maximum reduction of the parasite load in the population, and maximum effort to prevent or delay the spread of resistant parasites. Setting elimination as the main goal means that a number of parameters need to be clearly defined. Firstly, an elimination objective must have a timeline. The term ‘Western Cambodia’ must be also clearly defined. Falciparum malaria incidence and prevalence are considered relevant impact measurements. The objectives of the programme should be defined carefully, an overly ambitious target might lead to misinterpretation of a successful programme as failure. Absence of spread of artemisinin resistance should be considered as an important outcome measure of containment, although this may be difficult to assess in areas where there is little information (few data) on the current situation. In addition to the goals set by the Global Fund, specific targets and indicators should be set by the countries. The elimination goals require strong surveillance, based on passive case detection, active case detection, and identification of asymptomatic carriers using sufficiently sensitive tests. Evaluation of the RAI should include both performance indicators (e.g. each febrile case getting a proper diagnostic test and treatment) as well as impact measurements (falciparum incidence and prevalence) in its evaluation.

The second part of the discussion was dedicated to outlining the operational research that should be conducted within the context of ERAR. A short list was outlined as follows:

- mass drug administration (MDA) and targeted malaria elimination
- mapping passively and actively detected cases, including asymptomatic carriers;
- new treatment modalities including new chemical entities and extending ACT treatment courses to 5 or 7 days;
- molecular studies of resistant genes and gene flow, where the RAI can provide the infrastructure to collect paper filter blood samples;
- research aimed at methods on how to control vectors and how to eliminate transmission using pharmacologic approaches in the host (primaquine and/or ivermectin).

The TEG would like to see a mechanism by which its recommendations, after review and endorsement by MPAC, are communicated to the regional steering committee (RSC), in particular the operational research that should be conducted within the context of the RAI. This may be accomplished by the representation of WHO on the RSC.

Developments in study design and implementation of mass drug administration as a tool for eliminating artemisinin resistant malaria

The Mahidol-Oxford Research Unit (Bangkok) has recently obtained funding from the Bill & Melinda Gates Foundation (BMGF) and the Wellcome Trust for a study piloting targeted malaria elimination. It is planned to target mass drug treatment to villages/areas with high *P. falciparum* prevalence rates (measured by a large-volume qPCR method with a sensitivity of around 20 parasites/µl), with the objective of eliminating falciparum malaria from those villages/areas. It was noted that the proposed project, in this context, must be viewed as research and not as a policy recommendation. It will be important to assess not only the efficacy of the intervention, but also assess feasibility and acceptability,
which requires adequate engagement of the community. The intervention must also be assessed in the most at risk and vulnerable populations.

The main concern with this approach is how to deal with the ‘last man standing’ phenomenon, as the parasites not killed during the MDA campaign are likely to be the most resistant. An approach to avoid the ‘last man standing’ could be to give the 3 monthly courses of treatment with 3 different medicines. The TEG favored this approach and recommended modifying the protocol accordingly. The presence suspected piperaquine resistance in Western Cambodia raised the question of why this drug would be used for MDA in this area. The TEG stressed the need for better assessment of the strategies that work and those that are not working. Preliminary results of the study should be discussed during the next TEG meeting.

Provided funding is available, the next TEG meeting will be planned for February 2014 to include a joint session with the Chemotherapy TEG which is overseeing the development of the third edition of the Guidelines for the treatment of malaria. Some of the agenda points that will be addressed include updates on clinical studies of new antimalarial medicines, modeling piperaquine pharmacokinetics in extended course treatments, preliminary results from follow-up studies in South America on artemisinin resistance and preliminary results of the pilot MDA. The TEG members requested that elimination strategies of falciparum malaria in areas of artemisinin resistance in collaboration with WHO’s elimination team, as well as the approaches to address the failures of the present strategies, be the main topic for the next TEG meeting.
1. Welcome and introduction of new members

The TEG welcomed three new members:

- Siv Sovannaroth  
  National Center for Parasitology, Entomology and Malaria Control  
  Phnom Penh, Cambodia
- Nguyen Quang Thieu  
  National Institute of Malariology, Parasitology and Entomology  
  Hanoi, Viet-Nam
- Stephen Vreden  
  Academic Hospital Paramaribo  
  Paramaribo, Suriname

All members attended the meeting, except L. Conteh, who was unable to join for personal reasons. In addition, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United Kingdom Department for International Development (DFID), the Medicines for Malaria Venture (MMV), the Worldwide Artemisinin Resistance Network (WWARN) were invited as observers. Representatives of the Bill & Melinda Gates Foundation (BMGF), the US Agency for International Development (USAID), and the Australian Agency for International Development (AusAID) were also invited but were unable to attend. The full list of participants is provided in Annex 1.

2. Agenda and modus operandi

The meeting was divided in five sessions, each comprising one or more presentations followed by discussion (Annex 2). The background documents were made available to the TEG members two weeks ahead of the meeting (see list in Annex 3). All TEG members participating in the meeting submitted their declaration of interest, which was assessed by the Global Malaria Programme, Drug Resistance and Containment team. All the reported relevant interests were read to participants.

3. Minutes of the TEG 2012

The TEG 2012 meeting report was reviewed by the chair to highlight the recommendations that have had an impact and those that may need revisions (Annex 4).

4. Session 1: Update on artemisinin resistance surveillance

Is there evidence for the emergence of artemisinin resistance in South America?

Presentation

Data from the Suriname Bureau of Public Health shows a considerable and constant decrease in the number of malaria since 2000. In 2011, the number of malaria cases in the resident populations became too low for routine therapeutic efficacy studies (TES). As a result, the efficacy of artemether-lumefantrine was monitored in gold miners, despite the difficulty of ensuring a good follow-up in this population. A total of 74 patients were enrolled (M/F: 56/9, no children); of these 52 cases had day 3 data and only 11 were followed up to day 28. The adequate clinical and parasitological response was 100% at day 28 among these 11 individuals, but day 3 results showed 28% of patients with parasitaemia compared with 2% in 2005-2006. Slides were further assessed for quality and confirmation of results. Due to poor storage conditions, only 27 of slides taken at day 3 could be read by an expert microscopist, with day 3 positivity calculated to be around 16%. It must be noted that slides were declared positive
with counts as low as 1-2 parasites per 500 white blood cells (even lower when 500 fields were counted), which may be considered a lower than normal threshold.

Unlike Suriname, Guyana has not been successful in reducing malaria cases. *P. falciparum* and mixed infections increased from 39% in 2007 to 69% in 2011. Several TES of artesunate-mefloquine or artemether-lumefantrine in uncomplicated *P. falciparum* were conducted since 2004. The last study was conducted from May 2011 to July 2012; a total of 92 patients were enrolled with 68 followed up for 28 days. Failure rate at day 28 was 10.3%, but 63 out of 89 (70.8%) of day 3 slides were found positive. After quality control review, this proportion fell to 8% despite a sensitivity of 8 parasites/μl.

**Discussion**

While the malaria policy advisory committee (MPAC) as its meeting of March 2013 did not consider these findings as definitive evidence of artemisinin resistance, and that a designation as tier I was not justified, the TEG meeting of 2013 noted that there is a trend toward loss of efficacy based on day 3 positivity rate in Suriname, when data are compared with those of 2005-2006. It was recalled that artemisinin resistance started in similar pattern in Pailin. Fortunately, Suriname is implementing elimination measures, which encompass containment activities.

**Recommendations**

The TEG endorsed the proposal to conduct confirmatory studies in both countries and encouraged bordering countries, such as French Guyana, to conduct TES according to the WHO protocol 2009. The confirmatory study should include several measures to improve quality, including directly observed treatment, better patient follow-up and improved slide storage. Additionally, specimens for polymerase chain reaction (PCR) and molecular marker studies should be collected. Preliminary results from the follow-up studies in South America should be presented at the next TEG meeting.

The question of microscopy sensitivity threshold was addressed by the TEG. It was agreed that sensitivity levels should be according to current best practices recommended by WHO, and that only parasites with cytoplasm should be taken into account. Further research in the development of methods distinguishing dead from live parasites that can be used in routine surveillance studies would be useful. In particular, further studies will be necessary to confirm whether the absence of visible cytoplasm can be considered as an indication of a parasite being dead.

**Results of the TRAC study**

**Presentation**

Over the last 2 years the Mahidol-Oxford Research Unit (Bangkok), together with the London School of Tropical Medicine and Hygiene, the Liverpool School of Tropical Medicine and WHO, have coordinated a DFID funded trial with the acronym TRAC (Tracking Resistance to Artemisinins Collaboration). The study describes in detail the parasite clearance parameters (parasite clearance half-life and day 3 positivity) after a 3-day treatment regimen of artesunate (either 2 or 4 mg/kg/day), followed by a full-course of artemisinin-based combination therapy (ACT). The study took place in 13 sites in 8 countries in Southeast and South Asia (West Bengal, India; Ramu, Bangladesh; Shwe Kyin, Myanmar; Mae Sot Thailand; Srisaket, Thailand; Attapeu, Lao PDR; Pailin, Cambodia; Preah Vihear, Cambodia; Ratankiri, Cambodia; Pursat, Cambodia; Binh Phuoc, Viet Nam; Ranong, Thailand; Pyin Oo Lwin, Upper Myanmar), and in 3 sites in 3 countries in Africa (Kilifi, Kenya; Llorin, Nigeria; Kinshasa, Democratic Republic of Congo). Currently, 1247 patients have been included, representing 77% of the original target. Artemisinin resistance is arbitrarily defined in these studies as a parasite clearance half-life equal or greater than 6.2h, which is considered a conservative cut-off. Results of day 3 positivity rate are consistent with the results of clearance half-life, suggesting that the 10% threshold is for now
appropriate as an indicator of artemisinin resistance. It was also noted that the TRAC study provided material for molecular studies.

Discussion
The TRAC study has confirmed areas where slow clearance phenotype had emerged or identified new areas where increased vigilance is needed. The TEG members expressed the need for the TEG to be more engaged in discussions concerning tier designation criteria, and in the elaboration of resistance containment plans at country level. The recommendations on tier designation were discussed in Session 4.

Due to the loss in efficacy of dihydroartemisinin-piperaquine (DP) in the Western Cambodian area, atovaquone-proguanil has been used for first-line treatment as an interim solution. The TEG noted that it is imperative to replace atovaquone-proguanil with another first-line treatment since atovaquone-proguanil is like a monotherapy, vulnerable to resistance. The fixed combination of pyronaridine-artesunate appears to be the most appropriate medicine, but a study must be conducted to confirm its efficacy as the most recent data were obtained in 2007, and already indicated a 10% failure rate in Pailin. However, funding of this study has yet to be confirmed and the registration of the product by the Cambodian Health Authority is pending the results of the new study.

The TEG discussed the question of extending current ACT regimens from 3 to 5 or 7 days. This prolonged regimen could be an alternative in areas where ACTs are failing. An effectiveness and safety study using a 5-day regimen with artemether-lumefantrine at the recommended daily doses will be conducted in Myanmar. If the increased total dose displays signs of overcoming the problem of the failing partner drug, it is still unlikely that it will alter significantly the problem of artemisinin resistance. This is supported by the observations that higher total dose or longer treatment course (7 days) of artesunate neither modified the slow parasite clearance time, nor the success rate, which is still high even in the GMS. In addition, the extension of DP treatment to five days, with an increased total dose, raised safety concerns due to the risks of potentially serious QTc prolongation when the drug is administered with food.

Recommendations
The TEG concluded that the TRAC study results support the ≥ 10% day 3 positivity rate as a reliable threshold for detecting artemisinin resistance. Therefore, there is at the moment no need to update or re-define threshold recommended for confirmatory efficacy studies as provided by the TEG in 2012.

The TEG recommended replacing atovaquone-proguanil in Western Cambodia by another first-line treatment. The fixed combination of pyronaridine-artesunate appears to be the best option but a study must be conducted urgently to confirm its efficacy and safety.

The extension of the ACT regimen from 3 to 5 or 7 days, which could be an alternative in areas where ACTs are failing, will also require safety and efficacy studies. The TEG recommended that modeling of piperaquine blood concentrations should be conducted using an increased regimen of 5 days.

5. Session 2: Monitoring tools
Recent developments on assessing parasite clearance

Presentation
The parasite clearance curve is considered an important tool for measuring the therapeutic response of artemisinins. Existing methods for estimating the parasite clearance (PC) curve and derived summary values include plots of raw parasite count data, log-linear plots, and estimates of clearance rates normalized for initial parasite density. These methods share the same limitation of being primarily
graphical and difficult to quantify. Linear regression has been used to model clearance time, time to a 50% and 90% decrease in the parasite count, and parasite reduction ratios at 24h and 48h post treatment. A recent approach includes a ‘parasite clearance estimator’, developed by the WWARN for analyzing parasite clearance data. The PC estimator provides an estimate of the slope of the linear part of each patient’s log parasitaemia time curve. It determines a parameter called slope half-life (SLH), defined as the time needed for the initial parasite count to be reduced by half during the log-linear phase of parasite clearance curve. The existence of the initial ‘lag phase’ and the terminal ‘tail phase’ are determined and excluded from subsequent analysis of the data. Outliers are identified and also excluded from subsequent analysis. The parasite clearance rate constant (K) is estimated using a polynomial regression model (i.e. log transformed parasite count is modeled as a linear function of time) based on the selected subset of log-transformed parasite count data. The SLH is defined as log_e(2)/K.

Possible limitations about this methodology include:

- no estimate of K is possible if there are fewer than 3 non-zero parasite counts (including a zero replaced with the detection limit), which is the case with most routine TES studies;
- no estimate of K is possible if the initial parasite count is <1000/μl or the final parasite count is at least 1000/μl;
- the estimates of K and SHL are not applicable to the entire clearance curve, since the lag and tail phases as well as possible biologically implausible data are identified and eliminated;
- the software should be suitable for use in field settings where access to the internet and expert assistance may be limited.

An alternative methodology and software was devised, and has been tested on a representative sample of parasite clearance data provided by WHO. It has been implemented in an Excel®-based application after validation of the methodology. The methodology is appropriate for the case of at least three positive counts and for the cases of two or one positive counts. The methodology uses polynomial regression and makes two assumptions, or constraints, about the fitted PC curve - first that the slope is essentially zero (flat) at time 0, and second that the curve intersects the horizontal axis at the onset of the terminal zero phase. Thus the methodology was given the label “constrained polynomial regression”. The constrained polynomial regression was presented as detailed in the concept paper provided with the background documents.

This application was compared to the WWARN PC estimator using this data set and produced similar results. It was noted that in general the slopes derived by the two models correlate well (r = 0.90) and generated values of the clearance constant that are in the same range, except in a few cases. Reasons for discrepancies were illustrated using individual patient data.

Discussion
After discussing the significance of slow parasite clearance as an indicator of artemisinin resistance, methods based on using the slope of only the linear portion of the curve may miss important biological phenomena that occur in the tail phase. If artemisinin resistance is indeed attributable to genetic heritability the lag and tail phases could be important. The new tool incorporates these phases in the estimation of the parasite clearance constant. Additionally, the tool can provide PC estimates even when only few parasite counts are available, although the accuracy of these estimates may be reduced. The consensus was that the two methods should be rigorously tested to better understand their relative strengths and weaknesses. If both are proven valid, each may have a distinct role to play. It was agreed that the historical criterion of suspected resistance, parasite count 3 days after the initiation of treatment, should not be replaced at this time. Apart from the discussion about methods for assessment of parasite clearance slopes, several TEG members were of the opinion that characterization
of artemisinin resistance should not be limited to the PC slope, but should also take into account recrudescence after a prolonged course of oral artemisinin-based monotherapies.

Recommendation
It was agreed that the new tool would be tested by C. Plowe using the data from the Artemisinin Resistance Confirmation Characterization and Containment (ARC3) project to assess if the additional parameters are relevant for the parasite heritable part of the observed changes in the clearance curve in areas of artemisinin resistance. Other TEG members showed interest in testing this new tool on data generated in their respective settings.

**Update on molecular markers for artemisinin resistance**

Presentation
Molecular markers would be useful tools for surveying artemisinin resistance and targeting containment and elimination activities. Information on gene flow and parasite migration patterns may also help identify areas most likely to become new foci of resistance. Studies of parasite migration patterns throughout the GMS are underway.

In summary recent studies (see articles provided to the TEG members) move us closer to the goal of robust surveillance tools for measuring artemisinin resistance but more work is needed to accomplish this goal. The ARC3 genome-wide association studies (GWAS) identified two leading candidate resistance markers that are now being assessed in replication and field validation studies. The Cambodia parasite population structure study identified genetically distinct subpopulations of sensitive and resistant parasites in western Cambodia. New analyses that incorporate the results of population structure studies, initial and replication GWAS and signatures of selection studies should quickly lead to better understanding of whether artemisinin resistance spread from Cambodia to Viet Nam, Thailand and Myanmar, or whether it emerged independently in these or other sites. Moreover, the population genetics analyses provide a better means of controlling for population structure in replication GWAS studies, and thus may help confirm (or refute) current candidate resistance markers or identify new ones. The two related studies summarized here represent a high level of cooperation between clinical and laboratory-based scientists, public health officials and donors. Even closer cooperation could accelerate the identification and validation of resistance markers.

Discussion
The TEG discussed the result of these studies, and encourages the investigators to continue the validation studies and analyses. The ongoing studies in the GMS give an opportunity to collect filter paper blood spots for falciparum malaria patients, which can be used to do molecular analysis of genes of resistance and population structure. Although the identification of markers for artemisinin resistance is still in the research phase, a well-chosen set of single nucleotide polymorphisms (SNPs) will be able to define parasite populations highly likely to be artemisinin resistant, and will in addition provide insight into gene flow dynamics between parasite populations. This information has the potential for use in monitoring the spread and de-novo emergence of artemisinin resistance, and could be an important supplement to the more laborious parasite clearance studies. However, there are probably multiple SNPs involved (e.g. a mosaic of mutations associated with the phenotype that vary among parasite populations). The molecular analyses required for genotyping will likely be of high sophistication. The TEG can facilitate these by soliciting the help of centers of genomic research.

Recommendations
The TEG recommended that additional sources of parasites (e.g. rapid diagnostic tests, filter paper blood spot, and, if possible, blood depleted of white blood cells) should be sampled on a more routine basis
during TES and research trials, which could then be used for molecular analysis of genes of resistance and parasite gene flow studies.

**Update on in vitro susceptibility testing for confirming artemisinin resistance**

**Presentation**

The development of an in vitro susceptibility test would be useful to better define artemisinin-resistant phenotypes of *P. falciparum* in isolates. Depending on the assay used and study sites, previous in vitro and ex vivo studies using traditional growth inhibition assays have shown relatively good to virtually inexistent correlations between clinical outcome and in vitro or ex vivo results. A major challenge remains the sensitivity of some in vitro assays as well as the fact that the artemisinin-resistant phenotype could be characterized by a state of dormancy in the ring stage, rather than initial growth inhibition as primarily observed with most other antimalarial drugs. Parasites remain viable in spite of high drug concentrations and resume growth at a greater rate than susceptible parasite populations. Drug resistance could be mediated by a combination of decreased sensitivity of the ring stage to the induction of dormancy as well as a faster and higher rate of recovery from dormancy. A number of different in vitro drug susceptibility assays were adapted to the requirements of assessing factors contributing to artemisinin susceptibility: a standard 48h isotopic assay, a 72h ring-stage survival assay, a 72h mature-stage survival assay, a 6-day recovery assay, and a 9-day ring-stage growth arrest assay. While the 48h isotopic assay and the 72h mature-stage survival assay showed no evidence of differing susceptibilities to dihydroartemisinin across the two sites, the ring-stage survival assay consistently displayed higher survival rates at 72h with parasite lines from Pailin. The 6-day recovery assay showed a reduced initial slope of decaying parasitaemia as well as an earlier recovery from dormancy in parasites originating from western Cambodia.

**Discussion and recommendations**

Several in vitro methods for assessing artemisinin susceptibility are available for research purposes but there is no test available yet, which can be recommended as standard method. However, tests focusing on inhibition of ring stage development using short term (4-6 hours) exposure to artemisinins appear to have the best sensitivity to identify the resistant in vivo phenotype. In addition, multi-pulsing and 6-day (minimum) recovery assays are showing promise. It was also agreed that the definition of artemisinin resistance, sometimes based solely on delayed clearance by some authors, will become sharper as new standardized tools become available.

**6. Session 3: Modeling**

As an action item of the last TEG meeting, the Liverpool School of Tropical Medicine (I. Hastings) has undertaken a modeling effort using a population-genetic modeling approach. In this approach, depending on the epidemiological setting and treatment coverage, multiple first-line treatments (MFLT) do not always outlast an alternative strategy of sequential deployment of different ACTs. These conclusions are somewhat different to those reached by the group of R. Laxminarayan, which proposed a strategy of MFLT to slow down the emergence of resistance, based on a population biological modeling approach. These two approaches were presented and discussed.

**Presentations**

The team extended previous work that investigated the relative effectiveness of MFLT versus the standard sequential deployment of drugs in delaying the spread of drug resistance in falciparum malaria; this previous work suggested that MFLT out-performed standard sequential deployment until drug
coverage rate (the proportion of malaria infections treated) exceeded around 45 to 50% after which standard sequential deployment was slightly more effective. These simulations were re-run using new parameters and various scenarios, such as up to around 95% coverage. Standard sequential deployment still outperformed MFLT but the differences remained small and likely to be swamped by other factors, such as compliance. Standard population genetic models become unsatisfactory at very high drug coverage, and an ‘island’ model that allowed local malaria population extinction, re-colonization, and immigration was designed and implemented.

The methodology was extended to examine ‘antagonistic’ evolution of drug resistance where increasing resistance to one drug inevitably increases sensitivity to another drug. A one locus/two allele model is trivial: the policy should be to always use the drug where sensitivity is at its basal level or reduced by antagonism. The one locus/three allele situation is more plausible: one mutation increases resistance to drug 1 while increasing sensitivity to drug 2, while another mutation has the opposite effect. Standard sequential deployment always outperformed MFLT in these simulations. The explanation seems to lie in the fact that allele frequencies must sum to 100%. Sequential use means the current drug is selecting resistance to itself while driving out the wild type allele (sensitive to both drugs) and the mutation encoding resistance to the other, non-deployed drugs. MFLT means both drugs are present and mutations spread solely at the expense of the wild type. Similar results are obtained when these investigations were extended to a more complex 2-locus system. A methodology was designed, implemented and validated, but there was insufficient time to properly calibrate it.

The group of R. Laxminarayan used an evolutionary-epidemiological modeling framework for malaria and compared the benefits of different treatment strategies in the context of resistance evolution. This approach takes into account the parasite population sizes, which is relevant for different reasons, in particular the ‘last man standing’ phenomenon, where the last remaining parasites will be the most resistant. The MFLT strategy is understood as forcing the parasite to experience a diverse set of drugs in a short time to make drug resistance evolution difficult for the parasite. Unlike the population genetic model presented above, the population biology modeling method consistently showed that MFLT outperforms (better clinical outcome) sequential approaches, provided that coverage (f = fraction of symptomatic individuals that have access to and take antimalarial drugs) is high enough (> 50%).

These discrepancies may be due to the fact that the biology method tracks the absolute population size so that the numbers of infected individuals at any time point are known while the population genetic method does not account for the number of infected individuals at any point in time. The biology method explicitly tracks the absolute number of treatment failures in the population that result from drug resistance (i.e. total number of people not receiving treatment + total number of people receiving treatment but experiencing early/late treatment failure) while the genetic method cannot track the absolute number of treatment failures because changes in malaria prevalence are not tracked over time.

Discussion and recommendations
As the two models yielded divergent results on the benefit of MFLT in certain settings, the TEG could not give recommendations on the implementation of MFLT at this time. However the concept warrants further investment in research and modeling efforts and the TEG recommended that the modeling teams collaborate to understand the reasons for these differences. In future work, it will be important to address the problem of resistance to partner drug. If resistance to artemisinins exists, it is more likely that resistance to partner drugs will also develop, and vice versa. Consequently, resistance to ACT partner drugs is also an important concern and needs to be taken into consideration. The role of immunity and the notion of asymptomatic reservoir as well as the potential for cross-resistance should also be addressed. The benefits expected by MFLT should be well defined and these are expected to vary depending on the settings. National malaria control programme managers and the WHO group
responsible for treatment guidelines should be consulted before issuing any recommendations. Implementation of field studies in the near future would be useful to test the hypothesis. It was noted that MFLT is already a reality in some places, for example because different donors support the distribution of different drugs and, for this reason, a sequential deployment strategy may be difficult to implement in these countries. The use of a triple combination (three chemotherapeutic principles in a single therapy) as a means to delay resistance may be considered, while keeping in mind that once resistance has developed to this combination, the three chemical entities could be lost.

7. Session 4: Update on recent containment and elimination efforts

Emergency response to artemisinin resistance in the Greater Mekong subregion

Presentation
The presentation aimed at updating the TEG on recent activities resulting from the recommendations of the Joint Assessment, including the recently launched Emergency response to artemisinin resistance (ERAR) in the Greater Mekong subregion (GSM). This ERAR takes into account the recommendations issued from the first meeting of the TEG in 2012. A second component of this presentation was a discussion on the need to update the tiers based on the recent data. The new maps resulting from the discussion are provided in Annex 4.

The Joint Assessment of the regional response to artemisinin resistance conducted in 2011-2012 has helped galvanize political momentum to tackle drug resistant malaria in South East Asia. During the ASEAN Health Ministers’ Meeting, and ASEAN+3 Health Ministers’ Meeting held in July 2012, it was stated that antimalarial resistance is a regional concern. Later in November 2012 – the Declaration of the 7th East Asia Summit on Regional Responses to Malaria Control and Addressing Resistance to Antimalarial Medicines was endorsed by Heads of State/Government of ASEAN Member States, and several other countries. The political commitment has further translated into an important advocacy meeting hosted by Government of Australia in October 2012, at which time a Consensus on malaria control and elimination in the Asia-Pacific was adopted with a call for the creation of the Asia-Pacific Leaders Malaria Alliance (APLMA). The purpose of APLMA is to act as a high level advocacy platform, supported by two taskforces: the first one on access to quality medicines and other technologies, and the second on regional financing for malaria and other communicable disease threats.

The framework proposes 15 actions in 4 action areas, and is in line with the recommendations of the Global plan for artemisinin resistance containment. The framework will not replace existing national, regional or global strategies but aims at increasing coordination, quality and coverage of interventions. With regard to the field level activities, the framework focuses on action needed in tiers 1 & 2, as well as strengthening capacity and coordination at national and regional levels. WHO has received funding from AusAID and the BMGF to support the coordination of the regional response to artemisinin resistance from 2013 to 2015. A regional hub was established in Phnom Penh to strengthen coordination and technical support at regional and national levels. WHO will also host the secretariat for the regional steering committee (RSC) of the Regional Artemisinin Resistance Initiative (RAI) of the Global Fund (see below).

Discussion
The TEG discussed the ERAR, and recognized this is a framework for action, and thus not an action plan detailing and prioritizing interventions for implementation. Since addressing the problem of artemisinin
resistance ultimately requires elimination of falciparum malaria in regions with artemisinin resistance, the problem of asymptomatic carriers should also be addressed, which requires detection methods with adequate sensitivity.

Regarding the updating of tier designation and maps, the TEG will make recommendations but it recognized that the final decision on what actions to take is the responsibility of the national malaria control programmes. The tier designation should be based primarily, but not exclusively on day 3 positivity rates. Results of more detailed research studies and the place where artemisinin resistant parasite infection is suspected to have been acquired, may also be useful.

It was acknowledged that changing tier designation will have implications on the RAI. Maps will be prepared for the RAI; these will be released into the public domain after discussion with national malaria control programmes. In the future, a website containing updated data will be available, allowing the TEG members to re-assess and provide input if indicated.

Recommendations
WHO will continue to interact directly with the countries, to discuss any new data that could lead to a change in tier designation. A website containing updated data will be available, allowing the TEG members to re-assess and provide input if indicated.

From the review of current data, the TEG recommended that the following provinces should be designated as tier I: Bago East and Kayin provinces (Myanmar); Preah Vihear province (Cambodia). Kayah (Myanmar) is likely to meet the tier I designation but the recommendation is pending the availability of quality control of data from the TES. The district of Attapeu in Lao PDR, currently designated as tier II, may be changed to tier I after review of new data.

**Update on the recent call from the Global Fund on artemisinin resistance**

Presentation
The TEG was updated on the recently established RAI of the Global Fund. The RAI was built on the foundation of the ERAR. With this initiative approximately 100 million US$ will be allocated specifically for the regional containment of artemisinin resistance with activities in Cambodia, Myanmar, Thailand, Viet Nam, and Lao PDR. Country initial allocation of funding based on WHO gap analysis and criteria for defining success have been established as follows:

- **Myanmar and Lao PDR:** 35-40 US$ million
  - 75% reduction in cases and deaths from falciparum malaria.
  - 100% coverage of control measures, with a focus on artemisinin resistance areas
- **Cambodia:** 15 US$ million
  - Elimination in Western Cambodia
- **Viet Nam:** 15 US$ million
  - Full elimination
- **Thailand:** 10 US$ million
  - Full elimination

Another 15 US$ million will be allocated for regional activities, including cross border activities, monitoring and surveillance, technical and management support, and pharmaceutical regulation.

WHO consultants have been developing the concept note, with the assistance of key stakeholders in each country and liaising with the Global Fund secretariat around the templates, indicators, etc. The RSC will oversee the initial implementation but the specific arrangements will be made only after the terms of reference have been developed. It was emphasized that the RAI represents only 1 in 4-5 US$ of
the full funding requirement, making it imperative to continue dialogue with potential donors in order to fill all funding gaps.

Discussion
The TEG welcomed the additional funding for artemisinin resistance from the Global Fund. The overall aim is elimination of *P. falciparum* in areas of artemisinin resistance. The TEG reiterated that while the ultimate goal of containment efforts remains the elimination of falciparum malaria in areas with resistant parasites, the epidemiological realities in some countries such as Myanmar are such that interim objectives shall be containment of artemisinin resistant falciparum malaria, which is understood as maximum reduction of the parasite load in the population and maximum effort to prevent or delay the spread of resistant parasites.

Setting elimination as the main goal means that a number of parameters need to be clearly defined. Firstly, an elimination objective must have a timeline. The term of ‘Western Cambodia’ must be also clearly defined. Falciparum malaria incidence and prevalence are considered relevant impact measurements, but it needs to be recalled that elimination is not achieved by reduction to very low levels, but by complete interruption of transmission. Absence of spread should be considered as an important outcome measure of containment, although this may be difficult to assess in areas where there is little information (few data) on the current situation such as in Myanmar and several other countries. In addition to the goals set by the Global Fund, specific targets and indicators should be set by the countries. Elimination requires a strong surveillance, essentially based on passive case detection supplemented by active case detection. This approach could lead to the misperception of poor impact since strong surveillance results in more case detection and more treatments. Therefore, there is a need to find measurements other than case counting to assess impact. The Global Fund will consider performance outcome measure (e.g. each febrile case getting a proper diagnostic and treatment) as well as impact measurements (falciparum incidence and prevalence) in its evaluation. The potential utility of serological methods for identification of clusters (i.e. villages) where malaria is still transmitted has also been discussed. However no formal recommendations were formulated.

The second part of the discussion was dedicated to outlining the operational research that should be conducted within the context of ERAR. A short list was outlined as follows:
- mass drug administration (MDA) and targeted malaria elimination
- mapping passively and actively detected cases, including asymptomatic carriers;
- new treatment modalities including new chemical entities and extending ACT treatment courses to 5 or 7 days;
- molecular studies of resistant genes and gene flow, where the RAI can provide the infrastructure to collect paper filter blood samples;
- research aimed at methods on how to control vectors and how to eliminate transmission using pharmacologic approaches in the host (primaquine and/or ivermectin).

Recommendations
The TEG would like to see a mechanism by which its recommendations, after review and endorsement by MPAC, are communicated to the RSC, in particular the operational research that should be conducted within the context of the RAI. This may be accomplished by the representation of WHO on the RSC. It was therefore recommended that elimination strategies of *P. falciparum*, in areas of artemisinin resistance, be the main topic for the next TEG meeting.
8. Session 5: Mass drug administration

Presentation
The Mahidol-Oxford Research Unit (Bangkok) has recently obtained funding from the BMGF and the Wellcome Trust for a study piloting targeted malaria elimination. It includes mass drug treatment targeted to villages and areas with high \textit{P. falciparum} prevalence rates, with the ultimate goal of eliminating falciparum malaria from those villages/areas. \textit{P. falciparum} prevalence rates are being identified by a large-volume qPCR method with a sensitivity of around 20 parasites/µl. In villages where high carriage rates are being detected, targeted MDA to the population of those villages seems rational. The importance of these low parasitaemia needs further study. The project will assess the impact of three rounds of monthly administration of a full course of DP + primaquine on parasite prevalence during a one to two year follow-up period.

Discussion
It was noted that the proposed project must be viewed as research and not as a policy recommendation. All participants must provide written consent and all women of child-bearing age will be tested for pregnancy to comply with ethical norms. It will be important to assess not only the efficacy of the intervention but also assess feasibility and acceptability, which requires adequate engagement of the community. The intervention must also be also assessed in the most at risk and vulnerable populations.

To the question of how much resistance this research intervention could induce and how it could be measured, the investigators indicated that the study includes provisions for monitoring of molecular markers.

The main concern with this approach is how to deal with the ‘last man standing’ phenomenon as the parasites not killed during the MDA campaigns are likely to be the most resistant. The protocol should include provisions of a rescue treatment with drugs other than the ones used in MDA protocol. An approach to avoid the ‘last man standing’ could be to give the 3 monthly courses of with 3 different treatments. The TEG favored this approach and recommended modifying the protocol accordingly. The presence of suspected piperaquine resistance in Western Cambodia raised the question of why this drug would be used for MDA in this area.

Recommendation
The TEG stressed the need for better assessment of the strategies that work and those that are not working. Preliminary results of the pilot MDA should be discussed during the next TEG meeting.

9. List of annexes
Annex 1: List of participants
Annex 2: Agenda
Annex 3: List of documents
Annex 4: Minutes of the TEG meeting 2012
Annex 5: Tier maps
Addendum
TECHNICAL EXPERT GROUP ON DRUG RESISTANCE AND CONTAINMENT

27-28 JUNE 2013, CROWNE PLAZA HOTEL, GENEVA, SWITZERLAND

List of Participants

TECHNICAL EXPERTS

Arjen DONDORP, Chair
Mahidol-Oxford Research Unit
Bangkok, THAILAND

Kevin BAIRD
Eijkman Oxford Clinical Research Unit
Jakarta, INDONESIA

Karen BARNES
University of Cape Town
Cape Town, SOUTH AFRICA

Lesong CONTEH (unable to attend)
Institute of Global Health Innovation
Imperial College
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

James ELIADES
Mailman School of Public Health, Colombia University
New York, UNITED STATES OF AMERICA

Ian HASTINGS
Liverpool School of Tropical Medicine
Liverpool, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Corine KAREMA
National Malaria Control Programme
Kigali, RWANDA

Sylvia MEEK
Malaria Consortium
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
Harald NOEDL
Medical University of Vienna
Vienna, AUSTRIA

Chris PLOWE
University of Maryland
Baltimore, UNITED STATES OF AMERICA

Christophe ROGIER
Institut Pasteur
Antananarivo, MADAGASCAR

Allan SCHAPIRA
Independent Consultant
Manila, PHILIPPINES

Frank SMITHUIS
Medical Action Myanmar
Yangon, MYANMAR

Siv SOVANNAROATH
National Center for Parasitology, Entomology and Malaria Control
Phnom Penh, CAMBODIA

Julie THWING
Center for Disease Control and Prevention
Dakar, SENEGAL

Nguyen Quang THIEU
National Institute of Malariology, Parasitology and Entomology
Hanoi, VIET-NAM

Stephen VREDEN
Academic Hospital Paramaribo
Paramaribo, SURINAME

**INVITED SPEAKERS**

Scott FILLER
The Global Fund to Fight AIDS, Tuberculosis and Malaria
Geneva, SWITZERLAND

Mike WHITE
Independent consultant
Seattle, UNITED STATES OF AMERICA
OBSERVERS

Kasia STEPNIEWSKA
WWARN
Oxford, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Thomas KANYOK (unable to attend)
The Bill & Melinda Gates Foundation
Seattle, UNITED STATES OF AMERICA

Malcolm McNEIL
Department for International Development
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Timothy POLETTI (unable to attend)
Australian Permanent Mission
Geneva, SWITZERLAND

Trenton RUESBUSH (unable to attend)
USAID
Washington, UNITED STATES OF AMERICA

Tim WELLS
Medicines for Malaria Venture
Geneva, SWITZERLAND

WHO SECRETARIAT

Global Malaria Programme
Robert NEWMAN

Alison OSBORNE

Charlotte RASMUSSEN

Pascal RINGWALD

Lise RIOPEL

Marian WARSAME

Regional Office
Keith CARTER
Senior Advisor
Malaria and other Communicable Diseases
Washington, UNITED STATES OF AMERICA
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<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
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<tbody>
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<td>09:00–09:10</td>
<td>Welcome – Introduction and new members</td>
<td>Purpose of session and expected outcomes</td>
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<tr>
<td></td>
<td>A. Dondorp – Chair TEG DRC</td>
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<tr>
<td>09:10–09:20</td>
<td>Agenda and modus operandi</td>
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<td></td>
<td>P. Ringwald</td>
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<td>09:20–09:30</td>
<td>Minutes and action points last meeting</td>
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<td></td>
<td>A. Dondorp</td>
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<tr>
<td>09:30–10:30</td>
<td>Session 1: Update on artemisinin resistance surveillance</td>
<td>Discussion of the data regarding the status of artemisinin resistance. Feedback from the TEG on the proposed next steps as agreed to at an informal consultation held in Washington (21 Feb 2013) and at an AMI/RAVREDA meeting (8-11 April 2013).</td>
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<tr>
<td></td>
<td>i) Is there evidence for the emergence of artemisinin resistance in South America?</td>
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<td></td>
<td>P. Ringwald/K. Carter</td>
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<td>10:30 – 11:00</td>
<td>Coffee/tea break</td>
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<tr>
<td>11:00–12:00</td>
<td>ii) Results of the TRAC study</td>
<td>Update on the progress of TRAC.</td>
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<tr>
<td>Session 2: Monitoring tools</td>
<td>Purpose of session and expected outcomes</td>
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| 12.00–13.00                 | i) Recent developments on assessing parasite clearance  
M. White  
Discussion of current method(s) for assessing parasite clearance. |
| 13.00–14:00                 | Lunch                                    |
| 14:00–15:00                 | ii) Update on molecular markers for artemisinin resistance  
C. Plowe  
Update on recent findings. Recommendation on use of molecular markers in surveillance and interpretation of results. |
| 15:00–16:00                 | iii) Update on in vitro sensitivity testing for confirming artemisinin resistance  
H. Noedl  
Update on recent findings. Recommendation on next steps. |
| 16:00–16:30                 | Coffee/tea break                        |

**Session 3: Modelling**

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<tr>
<th>Time</th>
<th>Event</th>
<th>Note</th>
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| 16:30–18:00      | Multiple first-line treatments: outcome of recent modelling efforts  
I. Hastings  
A. Dondorp  
Discussion of modelling results. Feedback and recommendation on next steps. |
| 18:00–19:00      | Reception                                                            |                                                                      |

**Friday, 28 June 2013**

**Session 4: Update on recent containment and elimination efforts**

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<tr>
<th>Time</th>
<th>Event</th>
<th>Note</th>
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| 09:00–10:30      | Emergency Response to Artemisin Resistance (ERAR) in the Greater Mekong subregion  
C. Rasmussen  
Discussion of implementation of the ERAR. |
<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>10:30–11:00</td>
<td>Coffee/tea break</td>
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<td>11:00–11:45</td>
<td>Update on the recent call from The Global Fund on artemisinin resistance S. Filler</td>
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<td><strong>Session 5: Mass drug administration</strong></td>
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<tr>
<td>11:45–13:00</td>
<td>Developments in study design and implementation of mass drug administration/presumptive therapy for elimination as a tool for eliminating artemisinin resistant malaria A. Dondorp</td>
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<tr>
<td>13:00–14:00</td>
<td>Lunch</td>
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<td></td>
<td><strong>Closed session</strong></td>
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<tr>
<td>14:00–16:00</td>
<td>Formulation of TEG recommendations A. Dondorp</td>
</tr>
<tr>
<td>16:30–16:45</td>
<td>Coffee break</td>
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<tr>
<td>16:45–17:30</td>
<td>Adoption of TEG recommendations A. Dondorp</td>
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<tr>
<td></td>
<td>17.30 Closing remarks A. Dondorp/P. Ringwald</td>
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</table>
1  SESSION 1: UPDATE ON ARTEMISININ RESISTANCE SURVEILLANCE

Is there evidence for the emergence of artemisinin resistance in South America?


Results of TRAC study

Dondorp A. (2013). Results of the TRAC study

2  SESSION 2: MONITORING TOOLS

Recent developments on assessing parasite clearance


Update on molecular markers for artemisinin resistance


Update on in vitro sensitivity testing for confirming artemisinin resistance


3  SESSION 3: MODELLING

Antao T et al. (2012). The use of multiple first line therapies (MFT) to treat malaria in near-elimination scenarios.


4  SESSION 4: UPDATE ON RECENT CONTAINMENT AND ELIMINATION EFFORTS


5  SESSION 5: MASS DRUG ADMINISTRATION

Dondorp A. (2013). Mass drug administration

Minutes of the Drug Resistance and Containment Technical Expert Group

21–22 June 2012

Crowne Plaza Hotel, Geneva, Switzerland
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This meeting was funded by the Department for International Development (DFID).

The Global Malaria Programme would like to acknowledge with gratitude the contribution made by all the TEG members. The minutes were drafted by Amy Barrette, Lise Riopel and Charlotte Rasmussen and finalized by Lise Riopel.
## Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACD</td>
<td>Active case detection</td>
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<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
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<td>ARCE</td>
<td>Artemisinin resistance containment</td>
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<tr>
<td>AusAID</td>
<td>Australian Government Overseas Aid Program</td>
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<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<td>DFID</td>
<td>Department for International Development</td>
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<td>DRC</td>
<td>Drug resistance and containment</td>
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<td>ERG</td>
<td>Evidence review group</td>
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<td>FSAT</td>
<td>Focused screening and treatment</td>
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<td>GMS</td>
<td>Greater Mekong subregion</td>
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<td>GPARC</td>
<td>Global plan for artemisinin resistance containment</td>
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<td>IHR</td>
<td>International Health Regulations</td>
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<tr>
<td>LLIN</td>
<td>Long lasting insecticide treated net</td>
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<td>MDA</td>
<td>Mass drug administration</td>
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<tr>
<td>MFLT</td>
<td>Multiple first-line treatments</td>
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<td>MPAC</td>
<td>Malaria policy advisory committee</td>
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<td>MSAT</td>
<td>Mass screening and treatment</td>
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<td>NMCP</td>
<td>National malaria control programme</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<td>Pfmdr1</td>
<td>Gene coding for <em>P. falciparum</em> multidrug resistance 1</td>
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<tr>
<td>PHEIC</td>
<td>Public Health Emergency of International Concern</td>
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<tr>
<td>TEG</td>
<td>Technical expert group</td>
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<tr>
<td>TES</td>
<td>Therapeutic efficacy studies</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Summary and recommendations

Messaging and political commitment

The technical expert group (TEG) agreed on designating resistance to artemisinin\(^1\) and partner drugs a growing regional emergency that represents a major threat to global malaria control and elimination efforts if not contained and eventually eliminated. The TEG supports the prompt implementation of a strengthened regional emergency plan with an appropriate structure for monitoring its effectiveness, and rapidly responding to changes in the distribution of antimalarial drug resistance, and emphasizes that fighting antimalarial drug resistance must be a global effort starting with the implementation of the Global plan on artemisinin resistance containment (GPARC) recommendations in all endemic countries. The TEG considers strengthening and sustaining political commitment and awareness of artemisinin resistance in the Greater Mekong subregion (GMS) to be a high priority. The TEG determined it premature and currently inappropriate to call artemisinin resistance a “Public Health Emergency of International Concern” (PHEIC), following presentations by the Department of International Health Regulations (IHR) and the Global Polio Eradication Initiative. This view could change with time should circumstances change.

Global messaging will be developed using an evidence-based approach, with input from other partners across the Roll Back Malaria (RBM) partnership. Messaging should avoid both overstating as well as understating the problem of artemisinin resistance, and recognize that emerging resistance to certain partner drugs directly jeopardizes artemisinin-based combination therapy (ACT) efficacy in the region, and that no novel alternative antimalarial drugs are currently available and are unlikely to be available in the near future.

Definitions of artemisinin resistance

The flow chart in the meeting minutes (Annex 1) outlines the recommended steps required for the decision making process for the interpretation and response relative to therapeutic efficacy

\(^1\) Unless otherwise indicated, the word “artemisinin” is used in this document to refer to artemisinin and its derivatives, artesunate, artemether and dihydroartemisinin.
studies (TES) findings. To summarize, the proportion of patients positive on day 3 is a valuable, albeit imperfect, indicator for the presence of artemisinin resistance in a given population. If the proportion of patients positive on day 3 is > 10%, further investigation to confirm artemisinin resistance is warranted, including assessment of parasite clearance rate with a 7-day course of artesunate, or a 3-day course of artesunate followed by an ACT. The 10% threshold for the proportion of patients positive on day 3 will be re-assessed following modeling based on available datasets, and will consider the effect of the initial parasite density and the sample size of the study. In addition to baseline parasitaemia, it is also recommended that the interpretation of “day 3 positivity” rates considers trends over time and any changes in transmission intensity (which may affect study population immunity, which also influences parasite clearance rates). The proportion of treatment failure of an ACT is strongly associated with the efficacy of the partner drug. If TES of an ACT have failure rates of > 10%, studies on the efficacy of alternative ACTs to inform policy will be urgently needed and a new policy should be implemented as soon as possible.

Tier classification (as outlined in GPARC) should be made by national health authorities in collaboration with WHO, in consultation with the TEG. Tier I areas should be defined wherever resistance is confirmed or strongly suspected. The TEG recommends more vigilance regarding monitoring of artemisinin resistance and strict implementation of the GPARC recommendations in all areas, and recommends a wider area designated as tier II than currently applied, in order to widen the net to prevent spread of resistance.

*Artemisinin resistance outside the GMS*

There is no evidence currently available that indicates that artemisinin resistance exists outside the GMS. However, continued vigilance is mandatory.

*Improve existing containment tools*

Based on the experience of containment efforts to date, the elimination of certain foci of resistance can be envisaged in Cambodia, Thailand and Viet Nam. However, this will require the vigorous and simultaneous implementation of the most effective malaria control tools as outlined in the GPARC. While the ultimate goal of containment efforts remains the elimination
of resistant parasites, the epidemiological realities in Myanmar are such that interim objectives shall be containment of artemisinin resistant falciparum malaria, which is understood as maximum reduction of the parasite load in the population and maximum effort to prevent or delay the spread of resistant parasites. This will require:

- mitigation of the health effects in the affected populations;
- reduction of the parasite reservoir to the lowest possible levels;
- protection of mobile and migrant populations from infection;
- reduction of the receptivity and the vulnerability of threatened areas (i.e. tier II).

A regional emergency response plan is currently being prepared by the WHO Drug Resistance and Containment (DRC) Unit. The TEG expresses a keen interest to be involved in the preparation of the plan. The TEG recommended that the following components be particularly emphasized in the plan:

- community-based early diagnosis and treatment with follow-up wherever possible;
- mobile, migrant and marginalized populations;
- vector control (long lasting insecticide treated nets [LLNIs], long lasting insecticide treated hammock nets and personal protection).

Further recommendations will be made once the TEG reviews a draft of the plan.

**Potential novel containment tools**

The TEG identified the following potential novel containment tools:

- multiple first-line treatments (MFLT);
- extension of current ACT regimens to five days.

These two tools are promising and need urgent further evaluation.

**Gaps in research**

The TEG identified the following research priorities:

High priority:
• MFLT including statistical modeling; observational studies in areas with and without MFLT with molecular markers as indicators for drug resistance; operational aspects and feasibility;
• extension of current ACT regimens from three to five days;
• observational studies of artesunate efficacy in severe malaria, in areas affected by artemisinin resistance;
• primaquine use as a gametocytocidal drug (this will be discussed in a separate evidence review group [ERG] in August 2012);

Also considered important were:
• modeling of population movement to estimate the speed and magnitude of the spread of resistance in varying epidemiological settings using different interventions;
• further modeling of specific containment strategies which will be formulated in the emergency response plan;
• epidemiological and economic modeling of the regional consequences of resistance to artemisinin and partners medicines;
• evaluation of novel vector control methods, including the use of protective clothing for forest workers;
• entomological studies on transmissibility of artemisinin resistant *P. falciparum*; the mapping of *Anopheles* vectors and their resistance to insecticide; operational research on implementation of protective measures;
• use of molecular diagnostics as an epidemiological tool.

In addition the following ongoing research topics were considered of high importance:
• molecular markers for artemisinin resistance;
• new antimalarial drug development;
• behavioral research on mobile and migrant populations.
1. Meeting Background

1.1 Background
The TEG on drug resistance and containment is a standing committee established following the recommendations elaborated at the inaugural meeting of the Malaria Policy Advisory Committee (MPAC) to the WHO in January 2012. The TEG is tasked to advise MPAC on policy and recommendations regarding antimalarial drug resistance and containment. The specific roles and responsibilities of the TEG are described in the term of references attached in Annex 2. In brief, these include: evaluating the data being generated on drug resistance; providing evidence-based advice on standards for monitoring antimalarial drug resistance; providing recommendations on the strategies to detect drug resistance and to prevent its spread; and identifying research priorities on drug resistance and containment. MPAC will review the TEG recommendations, which are ultimately approved by the WHO Director General. The TEG is constituted of up to 15 members (currently 14), including a chair who is nominated for three years. The TEG will meet at least once a year, and whenever possible, will meet jointly with the standing TEG on chemotherapy.

1.2 Agenda and list of participants
The agenda and the list of participants are provided in Annex 3 and 4, respectively. All members attended except C. Karema, due to a conflicting meeting. The Australian Agency for International Development (AusAID), The Bill & Melinda Gates Foundation (BMGF), Medicines for Malaria Venture (MMV), UNITAID, and the World-Wide Antimalarial Resistance Network (WWARN) were invited as observers. Representatives of the Department for International Development (DFID) and United States Agency for International Development (USAID)/President Malaria Initiative (PMI) were also invited as observers but were not able to attend.

1.3 Modus operandi
There were two components to the TEG meeting: the first half day was devoted to presentations on Drug Resistance and Containment (DRC) Unit activities. The next one and a half day was devoted to interactive sessions. Presenters for each sessions are indicated in the
agenda. Recommendations were formulated by the TEG members during a close session at the end of the meeting.

2. Activities of the Drug Resistance and Containment Unit

2.1 Description of the unit
The DRC Unit was formed in October 2010, and currently comprises six collaborators: one coordinator, one team assistant, one medical officer and three technical officers. The DRC Unit is expected to: monitor drug resistance; communicate data to external partners with the goal of updating country drug policy; define product profile and research and development priorities; stimulate the innovation of tools and strategies for monitoring and containing drug resistance; and advocate and provide global coordination for the drug resistance containment plan. The DRC unit is working in close collaboration with the Regional Malaria Advisors of the six WHO Regional Offices as well as with international and national programme officers based in WHO Country Offices. Monitoring of drug efficacy is further strengthened by the contribution of regional networks in various part of the world. However, some of the regional networks are currently not active because of shortage of funding.

2.2 Monitoring the efficacy of antimalarial drugs
TES remain the most reliable tool to monitor antimalarial drug efficacy. Data from these studies are key drivers to policy change. The WHO protocol for surveillance of antimalarial drug efficacy has been subject to several revisions since its first implementation in 1964, which was then focused on detecting chloroquine resistance. In its latest and current version\(^2\), the protocol provides the same definition of treatment outcomes at all levels of transmission, allows for 28 or 42 days follow-up depending on which medicine is being tested and mandates the systematic use of polymerase chain reaction (PCR) to distinguish between recrudescence and re-infection. It is important to note that the assessment schedule provides information on

the proportion of subjects who remain parasitaemic at day 3 i.e. 72 hours following the initiation of treatment (known as “day 3 positivity” – see below).

A template protocol of TES is available in English and French languages\(^3\). The template offers several advantages: it meets ethical requirements of the Council for International Organizations of Medical Sciences (CIOMS) guidelines and is cleared by the WHO Ethics Review Committee. It provides standardized methods for the conduct, analysis and reporting of the study data with provisions for quality control and quality assurance. The protocol template also includes a data management system using MS Excel. It is programmed to perform real-time “per-protocol” and Kaplan-Meir analyses after double data entry is completed. The system is easy to use in settings with limited information technology (IT) infrastructure, allows export and import of data in and from different softwares, and facilitates feedback to WHO.

The WHO antimalarial drug efficacy database was built over the past 12 years and now includes approximately 4000 studies in 268,000 patients. The data come from the TES and other sources such as: published scientific literature and unpublished reports comprising information from Ministries of Health, national malaria control programmes (NMCPs), non-governmental organizations, research institutions and drug development partners. The recent WHO report on monitoring antimalarial drug efficacy accounts for 1120 studies in 81,848 patients and highlights the value of enhanced monitoring of antimalarial drug efficacy in updating drug policy and the early detection of artemisinin resistance\(^4\). WHO plans to make these data available online using a mapping system for which a website is currently under construction.

2.3 Building capacity for effective monitoring of antimalarial drug efficacy

In order to ensure that efficacy testing is implemented on a routine basis in all malaria endemic countries it is imperative to strengthen the capacities of the national teams involved in malaria control. In collaboration with WHO regional and country offices, DRC is providing support to

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NMCPs or partners in the implementation or monitoring of TES. Capacity building efforts aim at the proper implementation of TES, including accuracy and reliability of the generated data. Fourteen subregional network workshops on antimalarial drug-efficacy testing were organized between 2009 and 2011, covering more than 80% of all falciparum-endemic countries. WHO conducted training courses focusing on TES in seven countries. In addition, groups of clinicians and microscopists were trained as consultants in order to create a pool of regional experts who will provide technical support to countries conducting TES with the aim of ensuring high quality data. During the same period, WHO supported over 40 malaria endemic countries on issues regarding antimalarial drug efficacy, including technical advice on protocol development, data analysis, and the supply of quality-assured antimalarial drugs and/or PCR services.

2.4 Current global status of antimalarial drug resistance in P. falciparum

This section uses data published in the recent WHO report on antimalarial drug resistance, with updates where applicable.

Resistance of \textit{P. falciparum} to chloroquine is present in most malaria endemic areas. In Central America, presence of molecular markers of chloroquine resistance have been detected in Haiti, Honduras and Nicaragua. However, in Honduras and in Nicaragua, chloroquine remains fully effective clinically. Studies from China, Kenya, Malawi and Viet Nam suggest partial reversal of chloroquine resistance based on in vitro sensitivity testing and molecular markers of chloroquine resistance; however treatment failure rates with chloroquine remain high in China and Viet Nam.

The combination of artesunate with sulfadoxine–pyrimethamine is failing in many settings in Africa but is still highly effective in Afghanistan, India, the Islamic Republic of Iran, Pakistan, Sudan and Somalia. With the exception of West African countries, the combination of artesunate and amodiaquine is also failing in many areas. Comparison of treatment failure rates between patients treated with artesunate + sulfadoxine–pyrimethamine versus sulfadoxine–

pyrimethamine alone, and between artesunate + amodiaquine versus amodiaquine alone indicate that significant reduced efficacy of the partner drug (sulfadoxine–pyrimethamine or amodiaquine) results in reduced efficacy of the corresponding artemisinin combination therapy.

Although treatment failure rates reaching 10% have been observed with artemether–lumefantrine in Ghana and Burkina Faso, this combination generally remains highly effective in most of Africa. Likewise, artemether–lumefantrine is still effective in the GMS except in western Cambodia where treatment failure rates exceed 20%.

Mefloquine resistance is high in Cambodia and Thailand. In Myanmar and Viet Nam, treatment failure rates with mefloquine monotherapy in a dose of 15 mg/kg were high in early 2000; there are few recent data available from these two countries on the efficacy of artesunate–mefloquine combination or on *P. falciparum multidrug resistance 1 (Pfmdr1)* gene multiple copy number, a good marker of mefloquine resistance. However, high failure rates of artesunate–mefloquine are currently reported from the Thailand and Cambodia (both countries with presence of artemisinin resistance) suggesting that this combination may no longer be efficacious in these countries. Thailand is currently considering new treatment options, and Cambodia has changed its first-line treatment for uncomplicated falciparum malaria to dihydroartemisinin–piperaquine, except in Pailin, western Cambodia, where atovaquone–proguanil (see below).

Resistance to piperaquine was first reported in 1985 in the Southern provinces of China, where it had been deployed massively as a prophylactic and treatment intervention from 1974 to 1992. As much as 214 metric tons (equivalent to 140 million adult doses) were used during this period. An increase of the total adult dose to 1.5 g had little impact on treatment failures rates. Although the combination of dihydroartemisinin–piperaquine has only been introduced recently, there is a suggestion that this combination has reduced efficacy in some parts of western Cambodia (although the absolute numbers of patients studied remain small). Failure rates in Cambodia are currently not supported by in vitro sensitivity data for piperaquine, so more definite conclusions regarding the current situation of piperaquine resistance are pending. However, findings from studies in Pailin suggest that treatment failure with dihydroartemisinin–
piperaquine is associated with presence of a single copy of Pfmdr1, the major determinant of mefloquine sensitivity. Whether this implies exclusion of mutual resistance to mefloquine and piperaquine simultaneously is an important question for further study. Increased efficacy of artesunate–mefloquine observed in 2010–2011 in an area where treatment failure with dihydroartemisinin–piperaquine is high, supports this hypothesis. Dihydroartemisinin–piperaquine treatment failure rates ≥ 10% have also been reported in Rwanda and Papua New Guinea.

Pyronaridine was developed in China in the 1970’s, and used to treat acute uncomplicated and severe falciparum malaria starting in the 1980’s. Reports as early as 1982–1983 on cross-resistance between pyronaridine and chloroquine, piperaquine and quinine prompted the Chinese authorities to investigate and use pyronaridine in combination with several other drugs, including artemisinin derivatives. Artesunate–pyronaridine is a new fixed combination recently approved by the European Medicines Agency under article 58 for single course of treatment in areas with known resistance to other ACTs, and will be registered shortly in several malaria endemic countries where these conditions apply. In clinical trials, artesunate–pyronaridine showed therapeutic efficacy of 98%, except in Pailin, where treatment failures reached 10% after 42-days of follow-up.

The efficacy of atovaquone–proguanil can be easily compromised by resistance to atovaquone, which is associated with a single mutation in the gene coding for cytochrome b. Failures in prophylactic or curative use of this drug, as well as presence of mutations related to atovaquone resistance, have been reported from French Guyana, India, and in several countries in Africa. However, mutations related to atovaquone resistance have not been reported in South-East Asia. Atovaquone–proguanil is currently temporarily used as first line treatment on both sides of the border between Cambodia and Thailand in a limited area and under closely supervised conditions. This was decided because of high failure rates against the available ACTs in that region.

Artemisininin resistance is suspected or confirmed in four countries in the GMS: Cambodia, Myanmar, Thailand and Viet Nam. The proportion of “day 3 positivity”, a marker for suspected
artemisinin resistance, differs between individual sites. This partly depends on the ACT, since the partner drug contributes to some degree to the initial parasite clearance rate and thus the proportion of “day 3 positivity” could be affected if the partner drug is failing. Also, the dose of artemisinin derivatives used in the different studies varies between 2 and 4 mg/kg body weight per day, which has some impact on the initial parasite clearance in areas with emerging artemisinin resistance. Studies from the border regions between Cambodia and Thailand, and Myanmar and Thailand show reproducible results of increased proportions (> 10%) of “day 3 positivity”. Data reported from the border region between Myanmar and China need further confirmation. Proportion of “day 3 positivity” has reached a plateau in Pailin province over the past several years (around 50% of patients are still parasite positive at day 3).

2.5 Update on artemisinin resistance containment activities

The GPARC6 was launched in January 2011 with the overarching goal of protecting ACTs as an effective treatment for *P. falciparum* malaria. GPARC defines priorities to contain or eliminate artemisinin resistance where it already exists, or to prevent it where it has not yet appeared. These priorities are: stop the spread of resistant parasites; increase surveillance to evaluate the presence and spread of artemisinin resistance; improve access to diagnostics and rational treatment with ACTs and invest in artemisinin resistance-related research. Success of the implementation of these recommendations depends on the ability to motivate and coordinate action and mobilize resources.

The GPARC defines tiers based on the evidence of artemisinin resistance. Tier I areas are those for which there is credible evidence of artemisinin resistance. Tier II areas are those with significant inflows of people from tier I areas, including those immediately bordering tier I. Tier III areas are those with no evidence of artemisinin resistance and limited contact with tier I areas. Each country is expected to evaluate its level of risk and implement containment or control activities accordingly alongside appropriate monitoring and evaluation.

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The TEG called attention to the fact that the distinction in containment activities defined in GPARC between tier I and tier II is subtle. There is a need to increase the perimeter for containment around the areas where resistance is found, thus an increase of the tier I zones, since spread of resistance will first affect these adjacent areas. The TEG recommended that tier classification should be determined by the national health authorities in collaboration with WHO, in consultation with the TEG.

In tier I areas, an immediate and multifaceted response should be launched with the goal to contain and, if feasible, eliminate resistant parasites. This includes accelerated control to reach universal coverage, elimination of oral artemisinin-based monotherapies, focus on mobile and migrant populations, considering the use active case detection (ACD), mass screening and treatment (MSAT), focused screening and treatment (FSAT) and mass drug administration (MDA).

In tier II areas, the goal should be to intensify and accelerate malaria control activities, to implement specific tactics to manage the potential spread of resistant parasites from tier I with a focus on mobile and migrant populations, to actively eliminate the use of artemisinin-based monotherapies and intensify monitoring of therapeutic efficacy.

In tier III areas, the main goal is to prevent the emergence of artemisinin resistance through effective control measures with prompt parasitological diagnosis for all suspected malaria patients and effective ACT treatment for all confirmed cases, scaling up vector control, increasing routine monitoring of therapeutic efficacy and eliminating oral artemisinin-based monotherapies and poor quality drugs.

The GPARC was developed when the artemisinin resistance containment (ARCE) project was ongoing on the Cambodia-Thailand border. The ARCE project ran from 2008–2011. A number of key lessons were learned from the project. The project managed to rapidly increase access to prompt diagnosis and effective treatment – partly through an extensive network of village malaria workers in Cambodia. Banning oral artemisinin-based monotherapies as well as

enforcing the ban were successful in drastically reducing the number of offending drug sellers. Overall, the containment project proved very effective in lowering the burden of falciparum malaria in Pailin province. However, because of continued artemisinin drug pressure and by definition higher efficacy of ACTs against sensitive parasites, the proportion of artemisinin resistant infections among the remaining parasite population has increased in Pailin. This implies that ultimately containment can only be achieved through elimination of *P. falciparum* in areas of artemisinin resistance. A further key challenge for the project was to sustain initial progress. Very high coverage rates with LLINs were achieved, but maintaining the coverage was difficult, in part due to high population mobility.

At present, containment activities are ongoing in four tier I countries. In Cambodia, current containment activities are funded under the Global Fund round 9 programme. Activities in Thailand are ongoing in 22 provinces covering eastern and western Thailand and funded under the Global Fund round 10 programme. In Myanmar, the Ministry of Health and involved partners agreed on the Myanmar artemisinin resistance containment (MARC) framework in 2011 and activities started in mid-2011. In Vietnam, containment activities have only recently started.

A joint assessment of the response to artemisinin resistance in the GMS was conducted from November 2011 till February 2012, and was funded by AusAID and the BMGF. This assessment concluded that the general approach, as outlined in GPARC and several associated national level strategies and plans, is appropriate, but that the containment plans and strategies are not implemented with sufficient intensity, coverage and quality. The report from the joint assessment proposes ten fields of priority actions:

- intensify current field operations and manage them for results;
- strengthen leadership as well as coordination and oversight mechanisms;
- secure adequate financial resources;
- build political support;
- clarify and implement policy decisions on diagnosis and treatment;
- maintain, expand and improve drug efficacy surveillance networks;
• accelerate priority research;
• target migrant and mobile populations and engage with relevant employment sectors;
• prioritize Myanmar (while maintaining a strong response to artemisinin resistance in all GMS countries);
• engage with the pharmaceutical sector.

3. Artemisinin resistance: messaging and political commitment

3.1 The International Health Regulations
The IHR are a legally-binding global agreement about procedures to protect public health by preventing the international spread of disease\(^8\). The IHR result from direct instructions from Member States to the WHO secretariat (not the other way around). The Secretariat facilitates and advocates the implementation of the regulations by all parties, but has no power to enforce compliance or sanction non-compliance.

The IHR do not establish mechanisms for surveillance of drug resistance, nor are they intended to provide a framework for longer-term programmatic responses to specific diseases. However, drug resistance is a feature that may be considered in the assessment of events by Member States when deciding to notify WHO. IHR, through the obligations of States Parties, can contribute to the development of national capacities necessary for the identification and response to acute public health events.

IHR has several provisions for routine generic measures related to transportation, human travel, conveyances and points of entry. An example of measures related to travel is the obligation of yellow fever vaccination in travelers to and from yellow fever endemic areas.

IHR can include the following provisions:
• temporary recommendations lasting from 12 to 23 months maximum which are issued through a declaration of PHEIC and require advice from an IHR Emergency Committee;

- standing recommendations of indefinite duration, following advice from an IHR review committee.

In the context of artemisinin resistance, only standing recommendations would be relevant here, as this problem will remain beyond the time limit of 23 months.

A more flexible method of providing recommendations to governments, travelers and specialists in travel medicine is through the WHO publication International Travel Health (ITH). Some recommendations related to artemisinin resistance already exist in this document, which is updated annually\(^9\).

When considering measures related to travel, it is important to not only regard the scientific evidence base, but also consider the socio-political acceptability of measures, which are often viewed as punitive by the affected countries and populations. Efforts must also be made to minimize stigmatization in order to maintain the trust and cooperation of the affected countries.

In the context of artemisinin resistance it is not evident that declaration of a PHEIC mechanism or standing recommendation under IHR has added value in addition to clear and comprehensive WHO programmatic priorities offering evidence-based technical guidance for countries. For comparison, IHR are currently not used for addressing the problem of multidrug resistant tuberculosis.

### 3.2 The example of polio

The experience of the Global Polio Eradication Initiative was shared with the TEG. Obtaining an agreement on the declaration of polio as a “programmatic global health emergency” (which is not the same as a PHEIC) took several years of negotiation with partners and many consultations within the Executive Board, the World Health Assembly (WHA) and ad hoc bodies. Declaring a health threat as a global emergency raises high expectations regarding the full containment of the emergency; if this is not achieved the global community will consider this as

a failure. Emergency status also does not equate with financial support: for instance, the polio eradication programme has needed to scale back activities in 2012 due to funding gaps.

Durable political commitment is ultimately more important than using global emergency classification mechanisms. The declaration of a global health emergency is a slow process and cannot be imposed from outside the country by WHO or others; the countries themselves need to understand the nature and the magnitude of the health problem nationally and regionally. Polio was declared an emergency at a national level in several countries, before the WHA declared polio as a programmatic global health emergency.

3.3 Messaging and political commitment

While it may not be a PHEIC or standing recommendation under IHR, or a “programmatic global health emergency” (like the polio programme), artemisinin resistance is clearly a growing regional emergency with potential devastating global consequences if not contained and eventually eliminated. Artemisinin resistance in *P. falciparum* is currently suspected or confirmed in four countries (Cambodia, Myanmar, Thailand and Viet Nam). It is not known yet if the foci detected along the Myanmar-Thailand border represent spread or de novo emergence of resistance. Resistance to partner drugs (including amodiaquine, lumefantrine, mefloquine, piperaquine and sulfadoxine–pyrimethamine) has also been identified in several regions in South-East Asia, and development of resistance to the partner drug is facilitated by the presence of artemisinin resistance. Importantly, the combination of resistance to both components of ACT results in decreased efficacy of ACTs in parts of these countries, with no or very few alternative treatment options currently available for the treatment of *P. falciparum* malaria. It is thus important to note that artemisinin resistance is not just a problem of slower parasite clearance in the patient with malaria. This situation represents a major threat to global malaria control and elimination efforts. Myanmar has the highest malaria burden in the region, and — based on historical data on the spread of chloroquine and sulfadoxine–pyrimethamine resistance — is a potential gateway for the spread of artemisinin resistant parasites to Bangladesh and/or India and subsequently to Africa. Containment activities are ongoing in all four countries of the GMS but funding gaps and other constraints preclude full implementation,
especially in Myanmar and Viet Nam. Other constraints in some regions include extensive cross-border movement of mobile workers who have poor access to health services, widespread availability of oral artemisinin-based monotherapies and/or poor quality medicines, poor health infrastructures, and sub-optimal regional collaboration on both pharmaceutical regulation and malaria control activities.

Fighting antimalarial drug resistance must be a global effort starting with the implementation of the GPARC recommendations in all endemic countries. It is essential to increase implementation of prompt diagnostic testing, effective treatment and enhanced surveillance of malaria as well as strengthen routine monitoring for drug therapeutic efficacy in all malaria endemic countries.

With the commitment of partners, including AusAID, BMGF, DFID and USAID, an emergency response plan for the GMS is currently in development with a provision to include country-specific roadmaps. The coordination of the plan, for which WHO is responsible, will rest on five main pillars:

- strengthening leadership;
- improving drug efficacy surveillance networks and accelerating priority research;
- ensuring access to quality care for, particularly for migrants and mobile populations;
- facilitating implementation of containment activities in Myanmar and Viet Nam; and
- engaging the pharmaceutical sector.

Getting the messaging right is critical to galvanize the political commitment in affected countries, engage all key stakeholders, and mobilize resources. Good communication can rally support, build political commitment and secure the financial resources. Poor or uncoordinated communication can disrupt ongoing efforts, confuse partners and lead to adverse consequences. There will be a need to design a tailor-made set of messages in order to reach out to a broad group of stakeholders including governments of affected countries, donors and funders, inter-governmental platforms, industry partners, NGOs and the media.
Regarding messaging around artemisinin resistance, it is WHO’s aim to emphasize the urgency of the problem, which represents a major threat to global malaria control and elimination efforts. However, the message should not suggest that artemisinin resistance is unraveling the progress made towards global malaria control and elimination.

Points for consideration around messaging discussed by the TEG can be summarized as follows:

- ACTs are currently failing in a geographically limited region, where resistance to both the artemisinin and ACT partner drugs is present, causing severe and worrying limitations to the available treatment options for falciparum malaria in these regions. This message should be balanced against the fact that over 200 million people are successfully treated globally with ACTs each year, and that access to ACT treatment has contributed importantly to the current reduction in malaria morbidity and mortality. A general statement that ACTs are failing could endanger production and supply of ACT and reduce confidence in its use, jeopardizing the success achieved to date;

- Although the general content of messages around artemisinin resistance obviously needs to be consistent, messages need to be individually crafted towards funders, individual countries, NGOs, and other constituencies;

- Messaging should be encouraged, but stigmatization (for instance of migrant and mobile populations, or of Ministries of Health in countries with confirmed artemisinin resistance) should be avoided;

- Messaging would be stronger if the problem of artemisinin resistance was built on the foundation of mathematical modeling although calibration will be very challenging. In order to provide numerical data on this, modeling efforts will be conducted in several areas:
  - to make the investment case (deaths and/or DALYs averted in GSM, economic impact);
  - to clarify possible impact of spread or emergence in Africa;
  - to show how different interventions impact on malaria disease and economic burden.

- Messaging has to make use of clear statements, without oversimplifying the problem;
The TEG discussed whether messaging should convey that containment of artemisinin resistance is still feasible or that it is inevitable that artemisinin drug resistance will eventually emerge elsewhere, and that the current efforts are only buying time for the development of alternative antimalarial therapies. There are no current data to strongly support either view and the containment plans (GPARC) cover both scenarios. In both scenarios, containment efforts are essential since no novel alternatives medicines to ACT will be available for at least the next few (> 5) years;

The TEG also discussed whether the activities in tier I should be described as elimination or containment efforts. While elimination should be the end objective, it is clear that in certain settings such as Myanmar, elimination efforts will need to be preceded by a more realistic shorter term goal of malaria control aimed at preventing or delaying the spread of artemisinin resistance as well as reducing the parasite reservoir and decreasing the burden of disease;

It was noted that currently there is inadequate awareness about the magnitude, urgency and seriousness of the problem of artemisinin resistance in governments of some affected countries, even among senior Ministry of Health officials. Additionally, Ministries who have had negative experiences (e.g. with MDA) are likely to be less receptive to requests involving raising the alert level. The question of how to raise the level of awareness and obtain political commitment will need to be addressed at subsequent meetings.

Based on the above considerations, and following the presentations by the Department of International Health Regulations and the Global Polio Eradication Initiative, the TEG determined it is premature and currently inappropriate to call artemisinin resistance a PHEIC. The TEG agreed on designating resistance to artemisinin and partner drugs a growing regional emergency that represents a major threat to global malaria control and elimination efforts if not contained and eventually eliminated. The TEG supports the prompt implementation of a strengthened regional emergency plan with an appropriate structure for monitoring its effectiveness, and rapidly responding to changes in the distribution of ACT resistance.
4. **Review of current artemisinin resistance definition**

WHO recommends that each country should monitor the therapeutic efficacy of first- and second-line drugs every 2 years. This routine monitoring allows for:

- Assessment of treatment failures: treatment policy has to change when the treatment failure rate exceeds 10% by the end of follow-up (28 or 42 days, depending on the half-life of the drugs being monitored);
- Assessment of the proportion of patients still parasitaemic at day 3 (i.e. 72 hours after start of antimalarial treatment with ACT): studies conducted in GMS suggest that increasing prevalence of “day 3 positivity” is a useful indicator to detect emerging artemisinin resistance.

There is currently no consensus on the definition of artemisinin resistance. WHO is using the following working definition, which was used in the GPARC:

- an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
- a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence of parasites after day 7 within 28 or 42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance).

The proportion of patients who are parasitaemic after 3 days of treatment has been found to be a suitable though imperfect tool for screening for artemisinin resistance. It is highly dependent on several variables including the initial parasitaemia, acquired immunity against *P. falciparum* and skills of the microscopists; the efficacy of the partner drug influences also this measure. In studies with more frequent parasite counts, the parasite clearance half-life can be calculated accurately using the parasite clearance estimator recently developed\(^\text{10}\). This half-life, based on the slope of the log-linear parasite clearance curve, is unaffected by the initial

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parasitaemia. A drawback is that frequent (e.g. 6-hourly) sampling for assessment of parasite density is required, which will not be feasible in many settings. Measuring parasitaemia every 12 hours allows calculation of the parasite clearance rates but systematically overestimates the slope half-life compared to measurement made every 6 hours. High correlation between “day 3 positivity” rate and slope half-life was detected ($r = 0.88$) based on data collected during ARCE and coordinated by WHO. However, “day 3 positivity” is not predictive of treatment outcome when the partner drug used in the ACT is still effective. Despite high “day 3 positivity” rate, the number of patients failing after a treatment with ACT remains extremely low (2.5%) in areas of artemisinin resistance but with retained sensitivity to the partner drug.

In the current absence of a molecular marker for artemisinin resistance, artemisinin resistance is mainly defined by delayed parasite clearance. The current recommendation state that if > 10% of patients are still parasitaemic at day 3, more detailed studies to confirm the presence of artemisinin resistance in the area are needed. However, this confirmation should not delay containment activities. Based on initial modeling exercises, the TEG discussed whether the 10% threshold was too insensitive. However, data are still insufficient to recommend a new threshold, so the TEG recommends that NMCPs also considers an increasing prevalence of “day 3 positivity” a possible marker of artemisinin resistance, provided that study populations are similar, at least in terms of initial parasitaemia and level of acquired immunity.

WHO currently advocates confirmatory studies using a 7-day supervised course of artesunate monotherapy (4 mg/kg/day over 7 days) including:

- frequent blood sampling for parasitaemia (6- or 8-hourly) to calculate parasite clearance time, slope half-life and parasite reduction rate;
- plasma blood sampling (multiple) for artesunate and DHA concentration$^{11}$;
- whole blood sampling and depletion of white blood cells for genome sequencing; and

in vitro testing.

An alternative option is the 3-day course of artesunate monotherapy followed by a full (3-day) ACT course as currently used in the Tracking Resistance to Artemisinin Collaboration (TRAC) project. In contrast to the 7-day artesunate study, this approach does not provide information on treatment failure rates of artesunate monotherapy, but it can be disputed whether this information is essential for defining the presence of artemisinin resistance (as recrudescence with 7 day artesunate treatment were reported prior to the emergence of artemisinin resistance). While these approaches are generally considered acceptable and recommended, they are not always feasible due to ethical considerations or lack of research capacity – and they do not provide information on the efficacy of the treatment policies in use. As an alternative the TEG suggests that accurate assessment of the parasite clearance rate (at least 8 hourly) with 28 or 42-day efficacy with the ACT used or under consideration be monitored. It should be noted that the partner drug will have some impact on the initial parasite clearance rate.

The TEG emphasized that caution is required about the extrapolation of a definition of artemisinin resistance based on clearance data from South-East Asia to Africa. A threshold of 10% may not be suitable for Africa due to host immunity, even among young children. The TEG recommended that in addition to baseline parasitaemia, the interpretation of “day 3 positivity” rates should take into consideration the trends over time, and changes in transmission intensity over time (which may affect population immunity). The 10% threshold for “day 3 positivity” rate will be re-assessed following modeling and new evidence.

5. Artemisinin resistance outside Greater Mekong subregion

Published in vitro studies using artemisinin or artemether, and studies on SERCA type PfATPase6 polymorphism, reported to be linked to artemisinin resistance. These reports and other published clinical studies were presented to the TEG for review. This review of the literature detected only one clinical study reporting a parasite positivity rate at day 3 over 10%
in Indonesia. For most of the reports reviewed the TEG felt that methodology was flawed, data were too incomplete for assessment or that the evidence was at least inconclusive. Based on reviewed data, the TEG concluded that there is currently no evidence of artemisinin resistance in *P. falciparum* outside the GMS. However, the TEG recommends continued and intensified surveillance on ACT efficacy outside GMS and encourages consultation with the TEG whenever new data raise concerns.

### 6. Improve the use of existing containment tools

In areas with artemisinin resistance an immediate and multifaceted response is required. The recommended response is summarized in the GPARC document and reviewed in the “joint assessment report” mentioned above. A regional emergency response plan is currently being prepared by WHO, and the TEG should be closely involved in the reviewing and updating of this plan. Although it was not the aim of the current TEG meeting to review containment plans, several aspects of the response plan were briefly discussed by the TEG.

It was recognized that plans designed for regions with limited health infrastructure should focus on scaling up basic malaria control interventions such as early diagnosis and effective treatment, including rapid expansion of community-based approaches. Particular emphasis should be focused on vulnerable and mobile populations. The plan should also aim for universal coverage of vector control.

ACD, MSAT, FSAT and (focused) MDA are additional strategies mentioned in the GPARC for consideration. In September 2010, a consensus meeting on MDA was held. During MDA, every individual in a defined population or geographic area is required to take an antimalarial on a given day or over a given period of days. Although modeling suggests that repeated rounds of MDA could lead to elimination of the artemisinin-resistant strain, the meeting concluded

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that the repeated implementation, and achieving the high coverage required for elimination, would be difficult to achieve in most areas.

Improving access for migrant and mobile populations is a key pillar in the ongoing containment efforts. Current activities include distribution of hammock nets in Cambodia, distribution of nets through worksites, net loan schemes, training malaria volunteers among the migrant workers, piloting setting up screening points offering testing and treatment for malaria in areas such as bus terminals, and targeting migrants with behavior change communication. In addition, surveys and migrant mapping have been ongoing to collect information on migrants. The wide range of measures required to contain artesiminin resistance are known; however, resources being limited, the priority is now to identify interventions that need modification.

The TEG made the following general observations; additional recommendations will follow when the draft response plan is being discussed:

- Although elimination of artesiminin resistant parasites should remain the end goal for containment of artesiminin resistance, this should be preceded by realistic shorter term goals in settings where artesiminin resistance has emerged in a context of limited health infrastructure and malaria control measures. These more limited objectives should include prevention of and delaying spread of artesiminin resistance;

- An important component for formulating a response plan is addressing population migration. Implementation of basic control measures particularly in marginalized and migrant populations, is essential for prevention of spread of artesiminin resistant *P. falciparum*. Modeling using available data on population migration can be helpful to address this important factor. Getting technical support from geographers would be useful, as collecting reliable information on population movements is a challenge;

- Ownership of and responsibility for a malaria control programme by local, district, provincial and national health services is critically important;

- Providing access to prompt diagnosis and effective treatment, including the use of a community-based approach, is pivotal in any containment plan. Good coordination of village malaria workers and the use of mobile malaria workers is essential;
• It is important for the implementation of the GPARC to also focus on Africa. ACTs are being deployed on a large scale in Africa and there is a chance that resistance to artemisinin and/or partner drugs could also emerge there. Preventing spread from any foci where artemisinin resistant parasites emerge will be key to containment;

• In the absence of new drugs, strategies to halt the loss of ACT efficacy could include using multiple first-line antimalarial drugs, or prolonging the course of ACT treatment to 5 days. It has been shown that splitting the 6-dose regimen of artemether-lumefantrine over 5 days without increasing the total dose, improves drug exposure of lumefantrine and efficacy of artemether-lumefantrine. For other ACTs, if the total dose is meant to be increased, it is critical to conduct well-designed studies to assess the safety and the efficacy of prolonged ACT treatment, in particular, that of partner drugs.

7. Gaps in research for antimalarial drug resistance monitoring and containment activities

*Strategies requiring further modeling exercises*

Evaluation of multiple first-line treatments (MFLT) strategy with regards to:

• the effect of MFLT deployment on the risk of drug resistance (while this is expected to decrease resistance, some argue that it could in fact increase resistance);

• whether the risk of resistance is reduced most by using different ACTs sequentially or at the same time, same or different ACT in the private and public sectors or a different ACT in adults and children.

The preliminary modeling results shall be presented at the next TEG meeting and the recommendations discussed with the TEG on chemotherapy. It was noted that operational research on feasibility and implementation of MFLT is also essential.

*Modeling migration*

The effect on the spread of antimalarial resistance of both population migration and the effectiveness of various interventions targeted at migrant populations need to be included in ongoing modeling of containment strategies. There is a need to better understand migration of people across continents and migration of parasites (see above).
Economics
The economic impact of losing ACTs to resistance is thought to be huge, but it will be important to quantify this impact, even when confidence intervals are large. Modeling should include national, and if possible regional, health and economic impacts on individuals and health systems, comparing implementation of a regional emergency plan with current control measures. The analysis would draw on both epidemiological and cost data. The potential macro-economic losses of delaying containment are difficult to evaluate and could be explored as a separate analysis. The feasibility of calculating the costs of the spread of resistance to sub-Saharan Africa based on historical data for chloroquine and sulfadoxine–pyrimethamine resistance will be explored. Research groups best placed to conduct the necessary modeling of health and economic consequences of resistance both in Asia and Africa will be identified and the findings will be presented at a next TEG meeting.

Approaches to testing new drugs, regimens or combinations
Since reduced sensitivity to artemisinin may compromise the use of artesunate for the treatment of severe falciparum malaria, the TEG recommends establishing a registry system to monitor treatment outcome measures in patients treated with intravenous artesunate for severe malaria in tier I and II areas.

As noted above, a 5-day course of ACT could be evaluated in tier I areas, preferably in western Cambodia. Safety and tolerability as well as efficacy of a prolonged treatment course with an increase in total dose, in particular of dihydroartemisinin–piperaquine, need to be established in clinical trials. In areas such as western Cambodia, where patient numbers are small with almost no treatment alternatives, implementation and research can take place simultaneously.

Vector and entomology
Vector control is important and the only way to reduce the parasite biomass without increasing the antimalarial drug pressure. The TEG recommended entomology research projects addressing the following topics:
• mapping of *Anopheles* vectors and their capacity to transmit artesiminin resistant parasites; and in particular, whether the artesiminin resistant parasites are capable of infecting other main vectors such as *A. gambiae* and *A. arabiensis*;
• operational research on implementation of personal protective measures, especially in settings with outdoor biting vectors.

**Molecular markers**
There is currently a large research effort to identify a molecular marker for artesiminin resistance, and a validated marker could be available within the next 6 to 12 months. Once a marker becomes available additional research can be directed at developing easy to use methods, including from filter paper blood. As soon as a molecular marker for artesiminin resistance becomes available, the TEG will draft recommendations on sampling and monitoring strategies.

**Strategies for translating results of operational research into programme implementation for monitoring and containing resistance**
The TEG recognizes the importance of operational research for informing strategies to monitor for and contain antimalarial resistance. However, this should not delay implementation of containment measures, but rather be an intrinsic part of the implementation of the new interventions.

**Use of the gametocytocidal effects of primaquine as a containment tool**
An ERG on primaquine will take place in Bangkok in August 2012. The TEG recognizes the importance of this subject and would appreciate being informed on the outcomes of this meeting. The TEG called attention to the importance of using optimal study design to address the unanswered questions on the pharmacokinetics of primaquine.

**Monitoring effectiveness during chemoprevention interventions**
There are important study design questions to address for informing studies monitoring chemoprevention interventions (intermittent preventive treatment or seasonal malaria chemoprevention), including the definition of efficacy endpoints and impact (effectiveness). An
in depth discussion of this topic was beyond the scope of the current meeting and the TEG agreed that a dedicated group such as an ERG should address this topic.

8. **Formulation of TEG recommendations and next steps**

The TEG members formulated recommendations that are listed in the Summary and recommendations section of this report. The TEG also made the following suggestions for the next meeting:

- Representatives from NMCPs and research institutions from endemic countries in South-East Asia, and preferably those with experience in containment of antimalarial drug resistance, should be added to the TEG;
- The agenda of the current meeting was very full and the next meeting should provide more time for discussion;
- In situations where the WHO requires feedback on issues regarding antimalarial drug resistance or containment in between meetings, TEG members will be available to provide this.

9. **List of annexes**

Annex 1: Decision making for TES studies  
Annex 2: Terms of reference of the TEG  
Annex 3: Agenda  
Annex 4: List of participants
Annex 1: Decision making for TES studies

Day 3: % patients parasitemic

- < 10%
- ≥ 10% or < 10% but increasing over time

Day 28 or 42: % treatment failures

- < 10%
- ≥ 10%

Interpretation

- No evidence of resistance to artemisinin Partner drug is effective
- Suspected resistance to artemisinin Partner drug is failing

Response

- No change in treatment policy required
- Change ACT
- Confirm resistance to artemisinin No change in treatment policy required
- Evaluate alternative treatment options

*Day 3 parasite density interpretation to include an evaluation of: baseline parasitemia, host immunity, trends over time
Malaria Policy Advisory Committee

Technical Expert Group on Antimalarial Drug Resistance and Containment

Terms of Reference

I. Background and rationale
The Malaria Policy Advisory Committee (MPAC) has been constituted to provide independent advice to the World Health Organization (WHO) for the development of policy recommendations for the control and elimination of malaria. The mandate of MPAC is to provide strategic advice and technical input, and extends to all aspects of malaria control and elimination. MPAC can recommend that specific technical issues are analyzed through a time-limited Evidence Review Group (ERG) or a standing Technical Expert Group (TEG).

The MPAC recommends a standing TEG on antimalarial drug resistance and containment as there is now - and will be in the future - a continual need to review new evidence on drug resistance, make recommendations on necessary actions, and set research priorities.

II. Role and functions of the Technical Expert Group on antimalarial drug resistance and containment
The TEG on drug resistance and containment is tasked with reviewing evidence, providing guidance and making draft recommendations on issues of drug resistance and containment. The TEG is constituted by and reports to the MPAC. While the issue of resistance to artemisinins is of urgent concern, resistance to other antimalarials is also of prime importance.

As the issue of drug resistance and containment is evolving quickly, the TEG may provide advice directly to GMP when necessary.

The responsibilities of the TEG on antimalarial drug resistance and containment will be to:

• Evaluate the accuracy and integrity of data on antimalarial drug resistance, in particular data suggesting new foci of artemisinin resistance;
• Provide evidence-based advice on norms, standards and technical guidelines on monitoring of antimalarial drug resistance;
• Provide evidence-based advice on policies, strategies and approaches for drug resistance prevention and containment in general, as well as in specific situation. This includes:
  – Determining the triggers for emergency response related to the detection of artemisinin resistance or resistance to an ACT partner drug;
  – Provide recommendations, based on ongoing evaluation and evidence, on the effectiveness and impact of the implementation of strategies to detect, prevent and contain antimalarial drug resistance;
• Identify priority research areas in the field of drug resistance or containment.
III. Membership and structure of the TEG

The TEG will have up to 15 members. TEG members will serve in an independent, personal and individual capacity.

The TEG composition should strive for appropriate geographical representation and gender balance, and should comprise individuals representing different areas of expertise and experience within antimalarial drug resistance and containment.

Members of the TEG must have excellent technical knowledge, scientific publications in peer-reviewed journals and more than 10 years experience in at least one of the areas listed below.

The following areas of expertise should be represented in the TEG:

- Molecular markers of antimalarial drug resistance
- In vitro assays of antimalarial drugs
- *Plasmodium vivax* drug resistance
- Clinical trials of antimalarial drugs
- Pharmacokinetics of antimalarial drugs
- Modelling on malaria control and elimination
- Cultural geography or political science with a focus on population movement
- Entomology / vector control
- Public health economics

In addition, the TEG should include members who have worked or are currently working as national malaria control programme managers with experience in conducting routine monitoring of antimalarial drug efficacy, as well as general malaria control.

The TEG members will be selected by a nomination panel appointed by MPAC and GMP. Members of the TEG shall be appointed to serve for an initial term of up to three years, renewable once, for a period of up to an additional three years.

Membership in the TEG may be terminated by WHO, including for any of the following reasons:

- failure to attend two consecutive TEG meetings;
- change in affiliation resulting in a conflict of interest;
- a lack of professionalism involving, for example, a breach of confidentiality.

Prior to being appointed as a TEG member and prior to renewal of term, nominees shall be subject to a conflict of interest assessment by WHO, based on information that they disclose on the WHO Declaration of Interest (DOI) form (Annex 1). In addition, TEG members have an ongoing obligation throughout their tenure to inform WHO of any changes to the information that they have disclosed on the DOI form. Summaries of relevant disclosed interests that may be perceived to give rise to real or apparent conflicts of interest will be noted in TEG reports.

In addition, prior to confirmation by WHO of their appointment as TEG members, TEG nominees shall be required to sign a WHO confidentiality agreement (See Annex 2). Although all papers presented at the TEG may be made publicly available on the GMP website, pre-publication manuscripts or confidential documents will be clearly labeled as such and will only be provided to TEG members for discussion.
IV. Responsibilities of TEG members
Members of TEG have a responsibility to provide MPAC with high quality, well considered, evidence-informed advice and recommendations on matters described in these ToR. The TEG has no executive or regulatory function. Its role is to work with the GMP secretariat to provide draft recommendations to MPAC.

TEG members may be approached by non-WHO sources for their views, comments and statements on particular matters within antimalarial drug resistance and containment, and asked to state the views of TEG or details related to TEG discussions. TEG members should refer all such enquiries to WHO/GMP.

V. Structure
GMP will submit a nomination for the first chairperson of the TEG to MPAC for endorsement. The chairperson will serve for 3 years, renewable once. Future chairpersons will be selected from among the appointed TEG members. A rapporteur will be elected at each meeting. Drug Resistance and Containment unit, GMP will serve as secretariat for the TEG.

VI. Working Procedures
With the coordinator of the Drug Resistance and Containment unit, the chairperson of the TEG will develop a plan for routine operations of the TEG. The TEG will meet at least once per year and have additional meetings and/or teleconferences as needed. When practicable, the TEG meetings will be scheduled in association with meetings of the TEG on chemotherapy and will share a session with the TEG on chemotherapy. TEG meetings should be anticipated at least three months in advance of the meeting. WHO will provide support for travel and accommodation for the purpose of TEG meetings.

Decisions on TEG recommendations will, as a rule, be taken by consensus. In the exceptional situation that consensus cannot be reached the chairperson shall report the majority and minority views. It is also the chairperson's responsibility to ensure there is clarity for TEG members on what exactly is being decided.

A representative from the Medicines for Malaria Venture (MMV) and a representative from the WorldWide Antimalarial Network (WWARN) will be invited to participate as standing observers in the TEG meetings. WHO/GMP may also invite other observers to the TEG meetings, including representatives from non-governmental organization, international professional organizations, technical agencies, and donor organizations. Additional experts, and Technical Resource persons, may also be invited to meetings by the secretariat with approval of the chairperson, as appropriate, to further contribute to specific agenda items. However, only TEG members can participate in voting or decision by consensus. Observers shall not take the floor unless requested to do so by the chairperson and shall under no circumstances participate in the formulation of TEG recommendations.

Relevant staff from WHO Headquarters and Regional Offices will attend as members of the Secretariat.
VII. Dissolution of TEG
The relevance of the TEG will be assessed annually by the MPAC. The terms of reference will also be reviewed once a year by the TEG. Any proposed changes in the ToR must be submitted to and approved by the MPAC.
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<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>09.00 - 09.30</td>
<td>Welcome – Introduction&lt;br&gt;A. Dondorp - Chair TEG DRC</td>
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<tr>
<td>09.30 – 09.45</td>
<td>TEG DRC Terms of reference, declarations of interest, expected outcomes and modus operandi&lt;br&gt;P. Ringwald</td>
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<td>09.45 -10.00</td>
<td>Presentation of the Drug Resistance and Containment (DRC) Unit&lt;br&gt;P. Ringwald</td>
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<td>10.00 – 10.15</td>
<td>Coffee break</td>
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<td>10.15 - 11.00</td>
<td>Monitoring antimalarial drug efficacy&lt;br&gt;A. Barrette&lt;br&gt;Capacity strengthening&lt;br&gt;M. Warsame&lt;br&gt;Discussion</td>
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<td>11.00 – 11.45</td>
<td>Situation on artemisinin and other major antimalarial drugs resistance&lt;br&gt;P. Ringwald&lt;br&gt;Discussion</td>
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<td>11.45 – 12.30</td>
<td>Update on containment activities&lt;br&gt;C. Rasmussen&lt;br&gt;Discussion</td>
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<td>12.30 - 14.00</td>
<td>Lunch</td>
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| 14.00 – 16.00| **Session 1** – Artemisinin resistance: messaging and political commitment  
M. Hardiman, International Health Regulation  
B. Aylward, ADG Polio, Emergencies and Country Collaboration  
R. Newman, Global Malaria Programme  
Discussion | Salle Meyrin      | Expected outcome: Advise on what should be the message of WHO around artemisinin resistance and the development of an emergency plan. |
| 16.00 – 16.15| **Coffee/tea break**                                                |                   |                                                                                  |
| 16.15 – 17.30| **Session 2** – Review of current working definition of artemisinin drug resistance  
P. Ringwald  
A. Dondorp  
Discussion |                   | Expected outcome: Discussion on whether the definition should be changed and if so, on which basis. What are the current protocols used for screening and confirmation of artemisinin resistance and should these be harmonized including for Africa? By whom should the decision around Tier I, II, III mapping be made? |
| 17.30 – 18.30| **Session 3** – Artemisinin resistance outside Greater Mekong Sub-region  
P. Ringwald  
Discussion |                   | Expected outcome: Discussion on artemisinin resistance outside South-East Asia. What is the evidence? |
| 18.30        | **Reception**                                                        | Foyer             |                                                                                  |
| **Friday, 22 June 2012 – Salle Copenhague** | **Session 4** – Improve the use of the existing containment tools  
C. Rasmussen  
Discussion |                   | Expected outcome: Advise on future and ongoing containment activities with focus on: whether it is possible to improve the use of the available tools (case tracking, MSAT, FSAT), how better to target migrant and mobile populations, and how to improve the use of vector control in containment efforts. |
| 08.30 – 9.45 | **Coffee/tea break**                                                |                   |                                                                                  |
### Session 5 – Gaps in research for antimalarial drug resistance monitoring and containment activities

**A. Dondorp**

#### Expected outcome:
Recommendation on which topics should be further investigated and presented at the next TEG.

- Which strategies need further modelling:
  - Multi-drug first line;
  - Effect of population movement for spread of resistance (in various epidemiological/intervention scenarios);
  - Consequences over coming 20 years of failure of containment beyond Greater Mekong Sub-region with focus on India and Africa;
  - Country and region specific elimination/containment strategies.

- Approaches for testing new drugs in areas with artemisinin resistance
- Entomology studies (transmissibility of resistant parasites to Indian/African vectors)

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<tr>
<td>10.00 - 12.30</td>
<td><strong>Session 5</strong> – Gaps in research for antimalarial drug resistance monitoring and containment activities</td>
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<tr>
<td>12.30 - 14.00</td>
<td><strong>Lunch</strong></td>
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| 14.00 - 15.30 | Strategies for translating results of operational research and monitoring of resistance into programme implementation  
|               | Discussion on additional urgent research questions and funding strategies                        
|               | Use of primaquine for gametocytocidal effect                                                    
|               | Monitoring drug effectiveness during chemoprevention interventions (IPTi, IPTp, SMC)             |
| 15.30 - 16.00 | **Coffee break**                                                                                  |
| 16.00 - 17.30 | Formulation of TEG recommendations and next steps                                               |
|               | Dates and agenda of the next meetings                                                            |
| 17.30         | Close of the meeting                                                                             |
List of Participants

TECHNICAL EXPERTS

Professor Arjen DONDOORP, Chair
Mahidol-Oxford Research Unit
Bangkok, THAILAND

Dr Kevin BAIRD
Eijkman Oxford Clinical Research Unit
Jakarta, INDONESIA

Professor Karen BARNES
University of Cape Town
Cape Town, SOUTH AFRICA

Dr Lesong CONTEH
Institute of Global Health Innovation
Imperial College
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Professor James ELIADES
Mailman School of Public Health, Colombia University
New York, UNITED STATES OF AMERICA

Dr Ian HASTINGS
Liverpool School of Tropical Medicine
Liverpool, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Dr Corine KAREMA
National Malaria Control Programme
Kigali, RWANDA
Dr Sylvia MEEK  
Malaria Consortium  
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Dr Harald NOEDL  
Medical University of Vienna  
Vienna, AUSTRIA

Professor Chris PLOWE  
University of Maryland  
Baltimore, UNITED STATES OF AMERICA

Professor Christophe ROGIER  
Institut Pasteur  
Tananarivo, MADAGASCAR

Dr Allan SCHAPIRA  
Independent Consultant  
Manila, PHILIPPINES

Dr Frank SMITHUIS  
Medical Action Myanmar  
Yangon, MYANMAR

Dr Julie THWING  
Center for Disease Control and Prevention  
Atlanta, UNITED STATES OF AMERICA
WHO SECRETARIAT

Global Malaria Programme

Ms Amy BARRETTE
Technical Officer
Drug Resistance and Containment Unit

Dr Robert NEWMAN
Director

Ms Alison OSBORNE
Team Assistant
Drug Resistance and Containment Unit

Ms Charlotte RASMUSSEN
Technical Officer
Drug Resistance and Containment Unit

Dr Pascal RINGWALD
Coordinator, Drug Resistance and Containment Unit

Dr Lise RIOPEL
Consultant
Drug Resistance and Containment Unit

Dr Marian WARSAME
Medical Officer
Drug Resistance and Containment Unit

Ms Zsofia SZILAGYI
Communication Officer/advocacy
Director Office
Addendum*

Comparison of two methods of estimating parasite clearance rate following treatment of Plasmodium falciparum with artesunate

Parasite clearance half-lives were estimated using both the parasite clearance estimator developed by WWARN (available at: http://www.wwarn.org/research/parasite-clearance-estimator) and the parasite clearance estimator developed at the World Health Organization (WHO). We used ANOVA to assess heritability (H²) of parasite clearance half-life in identical parasite clones identified from among 304 samples from efficacy trials of artesunate and ACTs conducted in Bangladesh, Cambodia, Lao PRD, Myanmar, Vietnam, and Thailand. Clones were identical at the subset of 33,728 SNPs on a P. falciparum-specific Nimblegen DNA microarray that were neither heterozygous nor missing in all members of the clone group. Identical clones were observed among parasites from Cambodia, Lao PRD, Myanmar, and Vietnam. Two Cambodian sites shared identical clones, but no clone group contained parasites from different countries. Confounding factors that were significantly associated with the phenotype were included in final ANOVA models (e.g., log-transformed parasitemia at diagnosis), to yield adjusted heritability estimates. ANOVA was performed using SAS v.9.2. Clearance half-lives calculated by both algorithms were similar, as were heritability estimates based these half-lives (unadjusted WWARN H² = 0.66, p < 0.0001; WHO H² = 0.63, p < 0.0001). Half-lives adjusted for log-transformed starting parasitaemia were similar to unadjusted half-lives (adjusted for log-transformed parasitaemia at diagnosis WWARN H² = 0.63, p < 0.0001; WHO H² = 0.66, p < 0.0001). Half-life heritabilities were also similar in parasites from Cambodia and Vietnam (Cambodia: unadjusted WWARN H² = 0.61, p < 0.0001, WHO H² = 0.57, p = 0.0004; Vietnam: unadjusted WWARN H² = 0.65, p < 0.0001, WHO H² = 0.61, p < 0.0001). Half-life heritabilities in Myanmar were lower and not statistically significant, likely owing to a smaller sample size (Myanmar: unadjusted WWARN H² = 0.34, p = 0.10, WHO H² = 0.40, p = 0.07). There were only two clone groups with two clones each in Laos, which did not permit estimation of heritability at this site.

The scatter plot shows high correlation between WHO and WARN PC estimates : r²=0.905. Similarly the pairwise correlation (concordance) is also high: 0.952, p < 0.05.

The new estimator performed very similarly to the WWARN estimator, so ease of use could become one of the major reason for choosing one over the other.

* This comparison was requested by the TEG members and was performed by S. Takala, University of Maryland School of Medicine for the heritability and A. Barrette, GMP, for the correlation and concordance. The results were obtained after the meeting and were attached in the minutes as an addendum.