Minutes of the Drug Resistance and Containment Technical Expert Group
28-30 April 2014

Starling Hotel, Geneva, Switzerland
**Contents**

Acknowledgments ........................................................................................................................................ 3
Abbreviations ................................................................................................................................................ 4
Summary and recommendations .................................................................................................................. 5
Meeting Minutes ........................................................................................................................................ 10
1. Welcome and introduction of guest speakers .................................................................................... 10
2. Declaration of interest, agenda and minutes of TEG 2013 .............................................................. 10
3. Global Technical Strategy .................................................................................................................... 10
4. Session 1: Update on drug resistance .................................................................................................. 10
4.1 Tracking Resistance to Artemisinin Collaboration studies .............................................................. 10
4.2 Artemisinin resistance confirmatory study in Suriname ................................................................. 11
4.3 Antimalarial treatment policy change in Cambodia ........................................................................ 12
4.4 Update on K13 molecular markers ................................................................................................. 13
4.5 Update on artemisinin resistance definition and tier maps ............................................................ 15
5. Session 2: Modeling ............................................................................................................................. 16
5.1 Impact of spread of artemisinin resistance in Africa ....................................................................... 16
5.2 Multiple first-line treatments: outcome of recent modeling efforts ............................................... 17
6. Session 3: Update on recent containment and elimination efforts ................................................... 17
6.1 Emergency Response to Artemisinin Resistance project in the Greater Mekong subregion ........ 17
6.2 Update on the Regional Artemisinin Initiative .............................................................................. 19
7. Session 4: Elimination of artemisinin resistance in the Greater Mekong subregion ...................... 19
7.1 Mass drug administration pilot studies in the Greater Mekong subregion ..................................... 19
7.2 Malaria elimination strategies in the context of artemisinin resistance ........................................ 21
7.3 Vector control strategies in the context of artemisinin resistance .................................................. 22
7.4 Ivermectin ........................................................................................................................................ 23
7.5 Use of community health/malaria workers and volunteers for improved surveillance and response to support malaria elimination ........................................................................................................ 25
7.6 RTS,S/AS01 in low transmission settings for targeted elimination ................................................. 27
Acknowledgments

This meeting was funded by US Agency for International Development. The Global Malaria Programme (GMP) would like to acknowledge with gratitude the contribution made by all the Technical Expert Members on Drug Resistance and Containment (TEG) members and guest speakers Marc Coosemans, Kevin Kobylinski, Izaskun Gaviria, and Hannah Slater. The minutes were prepared by Lise Riopel.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>artemisinin-based combination therapy</td>
</tr>
<tr>
<td>APLMA</td>
<td>Asia Pacific Leaders Malaria Alliance</td>
</tr>
<tr>
<td>CHW</td>
<td>community health worker</td>
</tr>
<tr>
<td>DOT</td>
<td>directly observed treatment</td>
</tr>
<tr>
<td>ERAR</td>
<td>Emergency Response to Artemisinin Resistance</td>
</tr>
<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>GMP</td>
<td>Global Malaria Programme</td>
</tr>
<tr>
<td>GMS</td>
<td>Greater Mekong subregion</td>
</tr>
<tr>
<td>GTS</td>
<td>Global Technical Strategy</td>
</tr>
<tr>
<td>GWAS</td>
<td>genome-wide association study</td>
</tr>
<tr>
<td>IRS</td>
<td>indoor residual spraying</td>
</tr>
<tr>
<td>K13</td>
<td>gene on <em>P. falciparum</em> chromosome 13 encoding a Kelch protein</td>
</tr>
<tr>
<td>LC</td>
<td>lethal concentration</td>
</tr>
<tr>
<td>LLIN</td>
<td>long-lasting insecticide-treated net</td>
</tr>
<tr>
<td>MDA</td>
<td>mass drug administration</td>
</tr>
<tr>
<td>MFLT</td>
<td>multiple first-line treatments</td>
</tr>
<tr>
<td>MPAC</td>
<td>malaria policy advisory committee</td>
</tr>
<tr>
<td>MMW</td>
<td>mobile malaria worker</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>Pfmdr1</td>
<td>gene encoding <em>P. falciparum</em> multidrug resistance 1 protein</td>
</tr>
<tr>
<td>RAI</td>
<td>Regional Artemisinin Initiative</td>
</tr>
<tr>
<td>RSC</td>
<td>regional steering committee</td>
</tr>
<tr>
<td>SAGE</td>
<td>strategic advisory group of experts</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>TEG</td>
<td>technical expert group</td>
</tr>
<tr>
<td>TRAC</td>
<td>Tracking Resistance to Artemisinin Collaboration</td>
</tr>
<tr>
<td>VMW</td>
<td>village malaria worker</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Summary and recommendations

*Answers to malaria policy advisory committee questions*

The format of the summary and recommendations has changed compared to the previous TEG meetings. The TEG’s recommendations made specifically in response to questions posed by the malaria policy advisory committee (MPAC) including the major strategic issue of redefining containment in the light of recent epidemiological findings are placed separately in Annex 1. The summary and recommendations below partly overlap with these, but also cover additional issues discussed during the meeting.

“K13” molecular marker for artemisinin resistance

The recent discovery of a marker for artemisinin resistance in the gene located on chromosome 13 of *P. falciparum* encoding a Kelch protein (K13) has greatly impacted the field, including definitions of resistance and surveillance methods. The science around this new marker is quickly evolving and not yet fully understood. More than 30 different mutations in the K13 gene have been reported so far, not all of them being located in the resistance domains (presently thought to include amino acid positions ≥ 440), and different mutations may confer different resistance phenotypes. Given the significance of the discovery, its technical complexity and the rapidly growing information, the TEG expressed agreement for that an evidence review group (ERG) on the topic should be established to 1) to collect and review data; 2) to indicate which polymorphisms on K13 (and beyond) should have consequences, if detected in a given area, and describe these consequences; this includes a discussion on the development of integrated mapping of the relevant K13 mutations; 3) to propose organizational structures (such as a reference center) that can facilitate standardization of methods and information flow to national programs and WHO; 4) to identify remaining knowledge gaps for research. TEG recommended that future clinical studies, and all therapeutic efficacy studies, should include collection of (dry blood spot) samples for K13 assessment.

Definition of artemisinin resistance and consequences for the resistance tier-map

With the discovery of the K13 molecular marker, the definition of artemisinin resistance was adapted to incorporate K13 mutations:

Suspected endemic artemisinin resistance is defined as:
- a prevalence ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations; or
- a proportion ≥ 10% of patients still parasitemic on day 3 by microscopy; or
- ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:
- a prevalence of ≥ 5% of infections with strains containing Kelch resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with ACT or artesunate monotherapy.

The term ACT resistance should be applied only when the therapeutic efficacy of ACTs start to fail in the context of resistance to both artemisinin and the partner drug(s). ACT failures > 10% should prompt a change in policy with another ACT.
The new definition will impact current tier classifications. Pending new data from studies conducted in Myanmar, it is likely that in addition to the eastern provinces, the northwestern provinces of Myanmar will be classified as tier 1.

Furthermore, the temporal and spatial trends of findings on artemisinin resistance indicate that all falciparum endemic areas in GMS countries, which are not already affected by artemisinin resistance, are at high risk. The TEG recommends that all such areas should now be classified as tier 2. The strategies and interventions for these areas should be the same as for tier 1 areas, the only difference being a lower priority under financial and operational constraints.

**Multiple genetic lineages of artemisinin resistance in the Greater Mekong subregion**

Analysis of the recently identified molecular marker for artemisinin resistance showed that the C580Y mutation was the most prevalent in parts of the Greater Mekong subregion (GMS), but many other mutations in and near the K13 propeller region were also identified that are associated with resistance. Genetic analysis identified multiple genetic lineages of artemisinin resistance, suggesting that it is not only spreading but also emerging de novo, thus raising concerns about the effectiveness of a “firewall approach” (delaying or preventing spread from a focus) and giving further support to the advisability of eliminating falciparum malaria transmission in all areas of confirmed artemisinin resistance. The answers to the questions by MPAC (Annex 1) identify the implications of this strategic shift for the GMS. Prevention of spread of resistance from GMS, however, remains crucial because falciparum malaria is become increasingly resistant to the main new partner drugs (lumefantrine, mefloquine, piperaquine).

**Is there artemisinin resistance in South America?**

In Suriname, the study conducted to determine the presence of artemisinin resistance is still on going. Calculation of parasite half-life and molecular marker studies are needed before any further conclusions can be made.

**Treatment policy in Cambodia in the context of high failure rates of dihydroartemisinin-piperaquine**

In Cambodia, atovaquone-proguanil resistance conferring mutations were observed less than a year after the implementation of the drug as the first-line treatment in Pailin (2012) and tier 1 areas (2013), which emphasized the urgent need for policy change. For this reason, artesunate-mefloquine was reintroduced as first-line treatment in five provinces (tier 1), since the proportion of falciparum strains with multiple Pfmdr1 copy numbers (which confer mefloquine resistance) is currently minimal in the area. Quinine and doxycycline over 7 days has been adopted as rescue therapy. Dihydroartemisinin-piperaquine remains the first-line treatment in the rest of the country. Since resistance to mefloquine following its re-introduction is likely to reappear quickly, the TEG considers reintroduction of artesunate-mefloquine in western Cambodia a short-term solution. Artesunate-pyronaridine is currently being re-evaluated in Western Cambodia and may provide an alternative first line treatment for uncomplicated falciparum malaria in these provinces. Clinical studies (phase I and II) to assess the safety, efficacy, and effectiveness of a 5-day dihydroartemisinin-piperaquine treatment course were recommended. Future drug development should consider triple combinations of drugs with different modes of action, either with current drugs or by adding a new compound to some of the existing ACTs.
Impact of artemisinin resistance in Africa
Using current artemisinin and partner drug resistance data from Asia and Africa, five potential resistance scenarios were modeled to estimate the impact of artemisinin resistance on clinical incidence, severe incidence, and parasite prevalence in Africa. Scenarios with high levels of recrudescent infections resulted in far greater increases in clinical incidence compared to scenarios with high levels of slow parasite clearance. The model confirms the importance of protecting the partner drug, especially in Africa, which also emphasized the need to consider triple combination therapies. However, important issues, such as the choice of matching drugs, drug interactions and regulatory hurdles need to be addressed to take this further.

Update on current initiatives
Since the last TEG meeting in June 2013, the WHO hub for the Emergency response to Artemisinin Resistance (ERAR) has become functional, and the Global Fund US$ 100 M Regional Artemisinin Initiative (RAI) has started. A new multi-trust fund initiative, coordinated by the Asian Development Bank, is under way. TEG underlined the need for coordination between these initiatives and building synergy where possible. It was noticed that key representatives of these initiatives are already in close communication.

The TEG requested ERAR hub to prioritize the whole GMS mapping of which organizations are doing which activities in which areas targeting which population and in which time frame. This is a prerequisite for a further gap analysis regarding activities and funding.

To guide currently funded initiatives and those in the near future, TEG recommended urgent development of an action plan for elimination of P. falciparum in the GMS, which builds on the existing frameworks, but formulates and prioritizes concrete fundable activities.

Multiple first line treatments
The current evidence examining multiple first line treatments (MFLT) as a response to resistance is based on two modelling studies only and those gave contradictory conclusions. In the study which was found to support MFLT, the potential benefit the potential benefit was estimated to relatively minor; likewise the model that did not support MFLT also showed a small effect. Therefore, TEG cannot currently recommend adopting MFLT as a response to resistance but recognizes the need to be flexible and does not oppose such practice, in particular when it is already in place or when used to avoid drug stock outs. The TEG acknowledged that increasing the complexity of treatment policy risks practices that exacerbate rather than mitigate the problem. The potential benefit of doing so seemed insufficient justify recommending it. Measures to ensure drug quality and treatment adherence should be also emphasized.

Targeted mass drug administration as part of the malaria elimination strategy
Initial analysis of a pilot study using targeted mass drug administration (MDA) (3 rounds of a monthly full course of dihydroartemisinin-piperaquine) in villages with high malaria prevalence, show the expected results in reducing prevalent P. falciparum, but (as expected due to the untreated hypnozoite reservoir in the community) less so for P. vivax. Although not measured in that pilot work, success with MDA almost certainly depends on the coverage achieved, i.e. the proportion of people receiving therapy. The people most likely to be missed in MDA may also be the most likely to later reintroduce parasites into
their communities, i.e. mobile and migrant populations, or those frequenting the forest. This potential pitfall implies that a sufficiently large area has to be covered when implemented. The TEG considers that MDA can be useful as part of an elimination strategy if included in the context of a package of interventions. Several questions must be addressed to optimize targeted MDA trials, which include strategies for scaling up (such as blood volumes and sample sizes for screening and large scale community engagement, and acceptance and support). MDA remains a high-risk strategy, since it has the potential to increase drug pressure on the parasite population, driving increasing drug resistance (last man standing), so that efforts need to be maintained until elimination has been achieved. In principle, the drug used for MDA should be different than the ones used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. When possible, rotating the drugs used in MDA is recommended. The TEG recommends that more trials looking at various aspects of this strategy should be conducted as soon as possible and that national programmes and WHO should be involved in planning and evaluation with real-time sharing of information.

**Ivermectin as an adjuvant in elimination strategies**

The added value of ivermectin when combined with targeted MDA should be investigated. The TEG was encouraged by the widespread and apparently safe and effective use of this drug in MDA campaigns against onchocerciasis in western Africa. Entomological data from areas where ivermectin was deployed and safety data (in terms of highest tolerated doses) should be reviewed prior to MDA trials. Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration. The TEG also recommends other field studies with ivermectin given as MDA, but not necessarily in combination with antimalarial drugs.

**Effectiveness of repellents**

Malaria elimination in the GMS is challenged not only by drug resistance but also highly exophilic vectors. Results of a recent large study on the effects of personal repellents, in addition to long-lasting insecticide-treated nets (LLINs) on malaria transmission in Ratanakiri (eastern Cambodia), do not show an impact on overall prevalence (by real-time PCR) of either *P. falciparum* or *P. vivax*, likely because of poor adherence to the intervention. The TEG concluded that personal repellents couldn’t be recommended as a programmatic intervention in the GMS. Use of repellents can still be an important tool for individual protection in particular circumstances and there is still a scope for research on this tool and other anti-vector measures to address residual transmission.

**Role of village malaria workers and community health workers**

Village malaria workers (VMWs) and community health workers (CHWs) have important roles in several key areas of the response to artemisinin resistance, particularly in providing early diagnosis and quality treatment and behavioral change communication, surveillance and providing data for information systems, and in reaching migrant or mobile populations or hard to reach populations. Having VMW and CHW perform directly observed treatment (DOT) may be considered, in the context of the later stages of malaria elimination, when there are only a few cases left, and in non-mobile populations. In other settings, the TEG does not recommend a general emphasis on DOT, since at the population level the effectiveness of DOT for malaria treatment in the region has not been shown to be superior to non-supervised treatment. Research to identify other methods to improve adherence is important.
Role of malaria vaccines in elimination

There is currently insufficient data to suggest a role for the RTS,S vaccine in containment/elimination strategies. In the context of malaria elimination, all age groups should be vaccinated. The final formulation of the RTS,S vaccine has not been tested in South-East Asia. In addition, it has to be confirmed that RTS,S does not increase the asymptomatic *P. falciparum* parasite reservoir of transmissible parasites by inducing partial immunity. The TEG considered it important to invest in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.
Meeting Minutes

1. Welcome and introduction of guest speakers
All members attended the meeting, except K. Barnes and C. Karema. The Australian Department of Foreign Affairs and Trade, the Bill & Melinda Gates Foundation, the Global Funds to fight AIDS, Tuberculosis and Malaria (GFATM), the UK Department for International Development, the Medicines for Malaria Venture, and the US Agency for International Development were invited as observers. The full list of participants is provided in Annex 2.

2. Declaration of interest, agenda and minutes of TEG 2013
All members of TEG participating in the meeting submitted their declaration of interest, which was assessed by the Drug Resistance and Containment Unit at GMP and by Legal at WHO. All the reported relevant interests were read to participants. The agenda is provided in Annex 3. The TEG members endorsed the TEG 2013 meeting minutes.

3. Global Technical Strategy
The MPAC tasked GMP with the development of a Global Technical Strategy (GTS) for malaria 2016-2025. GMP and the Roll Back Malaria Partnership are working together to align the development of GTS and Global Malaria Action Plan 2. GTS will be launched jointly with Global Malaria Action Plan 2 further to its endorsement by the World Health Assembly 2015. A Steering Committee will provide guidance to GMP on the development of GTS to ensure that the process is rigorous and collaborative, involving consultations at all levels. WHO held the first series of consultations in October 2013 and seven regional consultations led by WHO Regional Offices are ongoing through June 2014. A GTS consultation website is available for contributing additional comments. The TEG members are encouraged to participate in the online consultation.

Discussion
TEG members welcome this initiative but stress the importance of ensuring harmonization between the GTS recommendations and those of TEG and other committees.

4. Session 1: Update on drug resistance
4.1 Tracking Resistance to Artemisinin Collaboration studies
Presentation
Tracking Resistance to Artemisinin Collaboration (TRAC) study monitors in detail the parasite clearance parameters (including 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 ACT. The main goal was to detect and map the spread of the delayed clearance phenotype defined as a parasite clearance half-life equal or greater than 5 hours. Since the last TEG meeting, analysis of mutations in and near the K13 propeller domains was also performed on samples collected from the sites participating in the study. Data on parasite half-life and K13 mutations from different study sites confirm the existence of artemisinin resistance in northern Cambodia and in Myanmar. Prevalence of K13 resistance mutations correlates strongly, but not always, with slow clearance. Data on delayed clearance phenotype from TRAC are consistent with those of WHO therapeutic efficacy studies. Molecular marker analyses showed that C580Y mutation was the most prevalent in parts of the GMS, but many other mutations in and near the
K13 propeller region were also identified that are associated with resistance. Molecular marker analyses of TRAC studies have also shown that low-level prevalence K13 mutations in Africa are not associated with slow parasite clearance. Overall, 3-day artesunate followed by an ACT is highly efficacious as measured by adequate clinical and parasitological cure rates between 95-100%, including dihydroartemisinin-piperaquine in areas where piperaquine resistance is found. The delayed parasite clearance phenotype was also associated with increased gametocyte carriage, but for the moment without evidence of resurgence of transmission.

Discussion
Higher cure rates observed in the artesunate plus ACT regimen could be due to the effect of 6-days artemisinin derivative, while the increased gametocytemia could result from not only artemisinin resistance, but also be due to failure of the partner drug.

Molecular and clinical studies must be seen as complementary. A number of samples have already been collected for K13 analysis. The spread of phenotypic resistance being associated with several independently occurring genetic polymorphisms and evidence that common mutations such as K13 C580Y are found in distinct genetic lineages in different geographic locations (see 4.4) means that artemisinin resistance is not only spreading, despite the vigorous efforts at containment, but also emerging de novo, thus raising concerns about the effectiveness of a “firewall approach” to containment of resistance (delaying or preventing spread from a focus) and giving further support to the advisability of eliminating falciparum malaria transmission in all areas of confirmed artemisinin resistance. Prevention of spread of resistance from GMS, however, remains crucial because falciparum malaria is become increasingly resistant to the main new partner drugs (lumefantrine, mefloquine, piperaquine).

Recommendations
A new strategy (further elaborated below) should be based on a principle of *P. falciparum* elimination in all areas of artemisinin resistance in GMS. One immediate measure should be change of the tier classification in GMS (see 4.5). All WHO-funded therapeutic efficacy studies should now include collection of samples for monitoring K13 mutations (this new requirement is communicated to national malaria control programmes through regional networks).

4.2 Artemisinin resistance confirmatory study in Suriname

Presentation
Further to TEG 2013 recommendations, a study to confirm artemisinin resistance was initiated in Suriname and bordering countries. The study employs a 3-day course of 4 mg/kg artesunate followed by one dose of mefloquine and one dose of primaquine, with 8-hourly monitoring of parasitaemia and follow-up until day 28. The study was initiated in July 2013 and 35 patients have been enrolled as of March 2014, with the majority coming from French Guyana. Of the 33 patients, who were followed-up to 72 hours, only 3 had positive parasitaemia on day 3. Only 7 patients have completed the study to day 28, all of whom had adequate clinical and parasitological response.

Discussion
The TEG noted that very low baseline parasitaemia could affect the sensitivity of the day 3 measurements. There is not enough information on study populations to implicate factors such as
immunity, which might explain the change in the day-3 positivity rate compared to 2011. The microscopy threshold of parasite detection is lower than in the WHO standard (100 fields read to consider a slide negative), as up to 500 fields are read before considering a slide negative.

**Recommendations**

Based on these data, it is still too early to determine whether artemisinin resistance is present in South America: calculation of parasite half-life and molecular marker studies are needed before drawing further conclusions.

**4.3 Antimalarial treatment policy change in Cambodia**

**Presentation**

Malaria cases and deaths have decreased steadily since 2000, but drug efficacy is rapidly lost to resistance. Atovaquone-proguanil was adopted as first-line treatment for falciparum malaria in Pailin Province in 2012 and in all tier 1 areas in 2013. Within 7 months of the introduction of this regimen, 5% of parasites sampled in Pailin harbored 268-cyt b mutation. In 2014, efforts to re-introduce artesunate-mefloquine as first-line treatment are in progress for 5 provinces, while dihydroartemisinin-piperaquine continues to be used in the rest of the country. The full implementation of the new policy is hindered by delayed registration and procurement of artesunate-mefloquine. The treatment failure rate with dihydroartemisinin-piperaquine is increasing despite adequate piperaquine plasma concentrations, suggesting high level resistance to this drug in Cambodia. New alternatives are needed to replace rapidly failing drugs. Therapeutic efficacy studies on artesunate-pyronaridine will start soon.

Despite the WHO recommendation for single low dose primaquine as gametocytocidal treatment in uncomplicated falciparum malaria in areas of artemisinin resistance, the implementation of a single low dose of primaquine as a transmission-blocking treatment in Cambodia has been delayed because of the perceived risks of hemolysis. Treatment policy must also take into account that treatment adherence is usually poor in the general population, especially among mobile and migrant populations. For this reason, DOT is considered a priority by the national malaria programme, provided that it is feasible, and that financial resources are available. The small number of malaria cases makes it difficult to conduct TES, and thus hinders timely surveillance to inform treatment policy.

**Discussion**

TEG is concerned about the complexity and the length of time it takes to change drug policy, and suggested it could facilitate the process by formulating specific recommendations.

For western Cambodia, the TEG supports the implementation of artesunate-mefloquine as a short-term alternative to the now failing dihydroartemisinin-piperaquine, but is concerned about the vulnerability of mefloquine. The re-introduction of artesunate-mefloquine makes sense at this time because the prevalence of pfmdr1 copy number has decreased; however, resistance is expected to re-emerge rapidly. For the time being, in case of failure of artesunate-mefloquine, quinine and doxycycline over 7 days is used as rescue therapy and the TEG endorsed this policy. The results of a study evaluating the efficacy of artesunate-pyronaridine in Western Cambodia may provide a new alternative for treatment.

The absence of new drugs is a major impediment in fighting antimalarial resistance. The TEG discussed alternative options. There was no consensus in the committee whether to recommend extension of dihydroartemisinin-piperaquine treatment from 3 to 5 days, because of potential safety issues regarding
the increased piperaquine dose (QTc prolongation). In clinical trials, piperaquine causes QTc prolongation in a dose-dependent manner, but within the recommended doses these effects are negligible; torsade de pointes has never been reported. Two independent modeling efforts yielded different predictions on piperaquine blood concentrations after a 5-day therapy; in one model the peak levels would not exceed 12% of the 3-day therapy and would remain below the threshold level for QTc prolongation, while in the second model, a more significant accumulation of piperaquine is predicted.

The TEG considered triple combinations of drugs with different modes of actions to be a target product profile for the next generation of antimalarial drugs, either using current drugs or by adding a new compound to some of the existing ACTs. The selection of drugs will require appropriate matching of pharmacokinetic profiles (linked to drug potencies) and investigation of potential drug interactions.

Based on a validated review of available data, WHO recommends a single low-dose primaquine course (0.25 mg/kg) as a transmission-blocking agent, as it was determined to be safe, even in the absence of glucose-6-phosphate dehydrogenase (G6PD) testing. However, given the evidence for risk of serious side-effects of the 0.75 mg/kg primaquine regimen, the Cambodian Ministry of Health is reluctant to implement this policy, and the national ethics committee demands a safety study in G6PD deficient patients. Such a study would take too long to conduct due to the small number of eligible patients. In the context of DOT in community and health facility settings, where safety can be monitored (urine), the administration of a single low dose primaquine to all patients treated with an ACT for falciparum malaria seems to be both reasonable and feasible.

**Recommendations**

Clinical studies (phase I and II) to assess the safety, efficacy, and effectiveness of a 5-day dihydroartemisinin-piperaquine treatment course should be carried out to enable an evidence-based recommendation in the near future. Assessment of effectiveness is important given the potentially low adherence to a 5-day regimen.

There is a desperate need to accelerate the development of new chemical entities. When new blood schizonticides become available, it will need to be analyzed, whether they would be used to best effect in triple combination with current ACTs or in new combinations, possibly with fewer therapeutic principles, but ones not affected by resistance.

The primaquine 0.25mg/kg regimen should be adopted in Cambodia with close real-time monitoring of safety through protocols, which can be applied in routine DOT in community-based and health facility services and in therapeutic efficacy studies.

### 4.4 Update on K13 molecular markers

**Presentation**

Mutations in the *PF3D7-1343700* Kelch protein (K13) have been associated with artemisinin resistance in vitro and in vivo. More than 30 different mutations in the K13 gene have been reported so far, not all of them being located in the propeller domains, and different mutations seem to confer different resistance phenotypes. Mutant K13 alleles are more prevalent in Cambodian provinces where resistance is prevalent, and the increasing frequency of a dominant mutant K13 allele correlates with the recent spread of resistance in western Cambodia. Strong correlations between the presence of mutations, in vitro parasite survival rates, and in vivo parasite clearance rates indicate that K13
mutations are important determinants of artemisinin resistance. Genotyping of this gene will be hugely important for large-scale surveillance, although replication and validation studies in other regions, in particular sub-Saharan Africa will have to confirm the association of these markers with the slow clearance phenotype in other parasite populations. Replication of the genome-wide association study (GWAS) studies using a gene-scan approach (evaluating association with parasite clearance half-life of any polymorphism versus no polymorphism in all genes) has confirmed K13 mutations as a major determinant of clinical artemisinin resistance in Cambodia, Viet Nam and Myanmar. GWAS of TRAC study samples also confirmed the role of K13, while suggesting that there are possible “permissive” or compensatory background mutations which could themselves spread and facilitate de novo resistance of K13 mutations. Parasites with a mutation in any of the K13 domains (presently thought to include amino acid positions ≥ 440) displayed longer parasite clearance half-life than parasites with wild type alleles; only a single nucleotide polymorphism (SNP) seems to occur in any given K13 gene; no parasite strain has shown multiple SNPs thus far.

Haplotype analysis revealed evidence for spread of K13 mutations (such as C580Y), as well as for independent emergence of the same mutation on different genetic backgrounds from distinct geographic areas, indicating that resistance is both spreading and emerging independently. There is some evidence of spread between Cambodia and Viet Nam; in contrast, the predominant K13 mutant found in Myanmar does not appear to have spread from Cambodia but likely arose independently.

**Discussion**

TEG concluded that K13 SNPs provide a useful and powerful new molecular marker of artemisinin resistance; nevertheless, further validation studies are needed to clarify roles of specific mutations.

The significance of mutations outside the K13 propeller domains, and of very low numbers of infections with K13 mutations in several African countries was discussed. If "paternity testing" of these variants (i.e. analysing genetic markers flanking the K13 gene to ascertain shared or different ancestral lineages) determines that they have spread from South-East Asia, it was suggested that new policies (e.g. triple therapy) should be considered for Africa to protect the available ACTs. It was noted, however, that evidence is not yet on hand to determine whether these rare mutants represent spread or de novo emergences, whether they are a new phenomenon or have been occurring all along in the background, or whether they threaten ACT efficacy.

**Recommendations**

K13 analysis should be part of all future clinical studies and therapeutic efficacy studies on falciparum malaria. However, the science around this new marker is quickly evolving. Given the significance of the discovery and the quickly evolving information on K13 mutations, an evidence review group on the topic should be established to 1) to collect and review data; 2) to provide guidance on interpretation of local data on K13 (and beyond) 3) to propose an organizational structure (including a reference center) that can facilitate standardization of methods and information flow to national malaria control programs and WHO; this includes the development of mapping of the relevant K13 mutations 4) to identify remaining knowledge gaps for research.
4.5 Update on artemisinin resistance definition and tier maps

Presentation

With the identification of the K13 mutations as a marker for artemisinin resistance, there was agreement that this definition needs to be updated, but it was thought that the clinical phenotype of slow clearance should remain part of the definition. Early reports of a background prevalence of around 2% of slow clearance in African settings in the absence of artemisinin resistance were taken as a guide for assessing the proposed cut-offs. As with the previous working definition, a distinction is made between suspected and confirmed artemisinin resistance. Thus a new set of definitions of artemisinin resistance was proposed to the meeting by the WHO Secretariat as follows (including minor editorial amendments recommended by the meeting):

Suspected endemic artemisinin resistance is defined as:
- a prevalence ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations; or
- a proportion ≥ 10% of patients still parasitemic on day 3 by microscopy; or
- ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with ACT or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:
- a prevalence of ≥ 5% of infections with strains containing Kelch resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with ACT or artesunate monotherapy.

The term ACT resistance should be applied only when the therapeutic efficacy of ACTs start to fail in the context of resistance to both artemisinin and the partner drug(s). ACT failures > 10% should prompt a change in policy with another ACT.

Discussion

TEG considers the new definitions based on genotype and phenotype prevalence appropriate in an epidemiological context. The sensitivity, although good, may not be sufficient to trigger alarm signals. The definitions will likely need adaptation with more data becoming available. Further research is needed (e.g. transfection studies) to clarify roles and relative importance of specific mutations that confer artemisinin resistance. The question of whether containment activities should be activated on the basis of “suspected” resistance should take into consideration a number of confounding factors affecting parasite clearance rate, such as immunity, or drug absorption and metabolism. However, artemisinin resistance confirmed with molecular markers should prompt containment activities.

Recommendations

WHO should prepare new recommendations for national programmes on resistance monitoring based on the revised definitions.

There is a need for a limited number of reference laboratories accredited by WHO for K13 sequencing, and details of structure and mechanisms should be indicated by the proposed ERG on the topic. It is emphasized that at the current stage of technological development, it would be counterproductive to aim at the establishment of these techniques in all endemic countries, considering that it is easy to
conserve and send dried filter paper blood samples safely. Where robust PCR capabilities are already established, impediments to exporting clinical samples can be addressed by shipping PCR-amplified material to sequencing centers. WHO should facilitate the collaboration between national programmes and reference laboratories.

The new definitions will impact current tier classifications. WHO is awaiting data from clinical studies and molecular analyses from three provinces of Myanmar before issuing maps on tier 1 and 2. However, the probability of including northwestern provinces of Myanmar in tier 1 is high. Meanwhile, the temporal and spatial trends of all findings on artemisinin resistance indicate that all falciparum endemic areas in GMS countries, which are not already affected by artemisinin resistance, are at high risk. The TEG recommends that all such areas should be classified as tier 2. The strategies and interventions for these areas should be the same as for tier 1 areas, the only difference being a lower priority under financial and operational constraints.

5. Session 2: Modeling

5.1 Impact of spread of artemisinin resistance in Africa

**Presentation**

Using current artemisinin and partner drug resistance data from Asia and Africa, five potential resistance scenarios were used to estimate the impact of artemisinin resistance on the incidence of clinical malaria, severe malaria, and parasite prevalence, if it were to exist uniformly across the continent. In the model, artemisinin resistance was characterized by slow parasite clearance while partner drug resistance was associated with late clinical failure or late parasitological failure. An individual-based malaria transmission model was used. Scenarios with high levels of recrudescent infections (treatment failures) resulted in far greater increases in clinical incidence compared to scenarios with high levels of slow parasite clearance. Across Africa, when partner drug resistance levels were estimated to levels similar to those observed for sulfadoxine-pyrimethamine, 39 million additional cases could occur over a five-year period; this represents a 2.7% increase compared to a scenario with no resistance. This suggests that partner drug resistance may result in greater increases in malaria morbidity than if widespread artemisinin resistance alone were to develop at the levels currently observed in Pailin. However, if artemisinin resistance levels increase, these results are likely to change. Unlike partner drugs, there are no available alternatives to artemisinin. This means that if artemisinin resistance does appear in Africa (or elsewhere); containing it could potentially be much more challenging than addressing partner drug resistance alone. This model has, however, some limitations: it assumes that resistance is static and uniform across Africa; there was no modeling of resistant and sensitive parasites, and, there was no consideration of the potential for resistance developing to one component of the ACT putting resistance pressure of the other drug.

**Discussion**

This modeling confirms that protecting the partner drug is critical for Africa. Consideration of triple combination therapies is important also in this context, but this approach requires careful consideration of which drug(s) can be added to an ACT.

The question of adding low dose primaquine as transmission-blocking agent in Africa was discussed, but it was considered that primaquine would have little impact in areas of high endemicity. Firstly, in high
transmission areas, resistant strains will generally be more transmissible and less affected by primaquine than the sensitive ones; secondly, lower proportions of infections are treated; thirdly, in the presence of partner drugs resistance, recrudescence is frequent but the possibility of re-treatment with primaquine is limited, because many recurrences are asymptomatic.

5.2 Multiple first-line treatments: outcome of recent modeling efforts
Presentation
In 2013 TEG discussed two mathematical models of implementation of MFLT as a strategy to reduce risk of emergence of resistance. The two models yielded divergent results, since the two approaches were built on somewhat opposing principles. For one group, MFLT justification found its source in an evolutionary principle, assuming that an organism (malaria) cannot evolve too many different niches (drug types), whereas the other group assumes that malaria can simultaneously evolve to all these niches, i.e. develop multidrug resistance. This last model found that a policy of MFLT outlasts sequential application provided drug coverage levels are low to moderate, and appears not to drive widespread multidrug resistance. Inadequate dosing (poor adherence) is a more potent driver of drug resistance than the MFLT or sequential policy. When simulations were done at high drug coverage, sequential use was slightly better (5%) than MFLT in this model, but the difference was negligible. The other model found that the benefit of MFLT (occurring at any coverage level) was also modest, not exceeding 10%.

Discussion
In Africa, where less than 40% of infections are treated, MFLT may have an advantage provided operational issues are handled properly and quality drugs are used, but in low transmission areas where resistance has not emerged, there is no good reason to promote MFLT. It was noted that the two models are not too far apart, and given the uncertainty of the impact and the difficulty of changing policy, it is not justified to recommend implementation of one or the other.

Given the limited size of these effects MFLT is unlikely to have an impact one way or the other and further efforts to reconcile the two model outputs may be futile. Factors such as adherence, supply chains, cost and toxicity are probably more important than policy choice.

Recommendations
TEG does not currently recommend adopting MFLT as a general response to resistance or a strategy to prevent it. There are however situations, where MFLT is justified for operational reasons, for example to avoid drug stock outs. Under all circumstances, measures to ensure drug quality and adherence to treatment should be emphasized.

6. Session 3: Update on recent containment and elimination efforts
6.1 Emergency Response to Artemisinin Resistance project in the Greater Mekong subregion
Presentation
Initiatives for containment of artemisinin resistance
Different initiatives have been launched for elimination and containment of artemisinin resistance in the GMS. These initiatives include the WHO project for technical support and coordination (ERAR), the GFATM’s RAI, and a newly established trust fund under the Asian Development Bank, and the Asia Pacific Leaders Malaria Alliance (APLMA).
WHO initiated the ERAR project with funding from the Australian Department of Foreign Affairs and Trade and Bill & Melinda Gates Foundation. The project aims to provide technical support, and support coordination of activities, for any initiatives and partners as needed. To do this, WHO has established a regional hub in Phnom Penh, Cambodia, and has staff in country and regional offices to provide technical support across the GMS. Key activities from the 2014 workplan were presented to the TEG for each of the six ERAR project objectives:

1. Strengthen leadership, coordination and oversight mechanisms;
2. Maintain and expand drug efficacy surveillance networks and accelerate priority research;
3. Improve access for migrant and mobile populations to quality services;
4. Facilitate the full implementation of the Myanmar Artemisinin Resistance Containment framework;
5. Strengthen the response to artemisinin resistance in Viet Nam;
6. Limit the availability of oral artemisinin-based monotherapy, substandard and counterfeit antimalarial medicine while improving quality of ACTs.

RAI is funding activities in five countries from 2014 to 2016, in addition to a regional component. RAI is overseen by a regional steering committee (RSC), supported by a secretariat located in the ERAR regional hub in Phnom Penh. APLMA was established to promote regional political leadership and collaboration against malaria in Asia and the Pacific. The alliance is hosted by the Asian Development Bank and has task forces on 1) quality medicines and other technologies, and 2) regional financing for malaria and other health threats.

**Epidemiology**

According to national estimates, a total of 47 million people are at risk of malaria across Cambodia, Lao PDR, Myanmar, Thailand and Viet Nam. The number of reported deaths, as well as the total number of reported cases (presumed and confirmed) has been falling. To a large extent, regional trends have been influenced by the significant reductions in incidence in Myanmar since 2011. In Cambodia, reported malaria cases have also been falling. In Lao PDR, malaria epidemics among migrant and mobile populations have occurred recently in the southern part of the country. In Thailand, data from partners working along the border with Myanmar have been included only since 2011 leading to an increase in the total reported cases. In Viet Nam, the number of cases has been falling slightly but appears relatively stable at a low level. Two of the six countries in the GMS have longer-term national strategies with formulated goals for national malaria elimination: China aims to eliminate malaria by 2020, and Cambodia aims to eliminate *P. falciparum* malaria by 2020, and all other malaria species by 2025. National strategies in the remaining four countries cover only the period until 2015 or 2016, and none of these strategies have explicit objectives for national elimination.

**Discussion**

TEG underlined the need for the ERAR hub to ensure effective coordination between initiatives to avoid duplication, to liaise with already funded activities such as the RAI, and build synergy where possible. The quality of epidemiological data continues to be in question: providers of ACT (public and private) could be included as a source of information. The ERAR hub was requested to prioritize a mapping for the whole GMS of which organizations are doing which activities in which areas targeting which
population and in which timeframe. This is a prerequisite for a further gap analysis regarding activities and funding.

**Recommendations**

Donor funding should not be limited to current tier 1 provinces. The priority is to have good services in tier 1 and the second priority is to have the same in tier 2 provinces. Information available on mobile and migrant population needs to be integrated into future strategies. The ERAR hub should report on its activities and progress at the next TEG meeting.

### 6.2 Update on the Regional Artemisinin Initiative

**Presentation**

In March 2013, the GFATM Board allocated US$ 100 million for three years in response to the need for a supra-national approach addressing artemisinin resistance in the GMS. The RAI includes US$ 15 million for an inter-country component and US$ 85 million for country components in Cambodia, Lao PDR, Myanmar, Thailand and Viet Nam. Total cost of LLINs represent 25% including the procurement and supply costs. The principal recipient (UNOPS) has disbursed first installments to Lao PDR, Myanmar and Thailand. Disbursements to Cambodia and Viet Nam are pending. The inter-country component is expected to start in July 2014. The GFATM sees APLMA as the political arm of the RAI while ERAR is seen as the technical arm. The RAI is overseen by a RSC consisting of representatives from: country coordinating mechanisms, national malaria control programmes, civil society, private sector, the Association of Southeast Asian Nations (ASEAN), the Asian Development Bank, development partners, WHO and academia. Following a RSC meeting in September 2014, the GFATM will negotiate year 2 workplans and budgets in November 2014. Any reprogramming suggested by the RSC can be included during in this process. As with any other grant, the principal recipient is responsible for monitoring and evaluation. The RSC also wants a higher-level monitoring and evaluation group working with the ERAR hub.

### 7. Session 4: Elimination of artemisinin resistance in the Greater Mekong subregion

#### 7.1 Mass drug administration pilot studies in the Greater Mekong subregion

**Presentation**

The targeted malaria elimination project is a multinational trial of targeted MDA in areas of high malaria prevalence. Obtaining approval for implementing these studies was challenging. Community engagement must be a big part of the effort. Targeted malaria elimination project sites are located in three distinct regions: western Cambodia (Pailin), the border between Thailand and Myanmar, and Viet Nam. The rationale for MDA and preliminary results of the pilot studies in four villages located in Kayin state, Myanmar near the Thailand border were presented. The protocol consists of a monthly course of dihydroartemisinin-piperaquine with one dose of primaquine for three months (except in Cambodia where primaquine is not approved for blocking transmission). Two villages had the MDA intervention with treatment described above and two control villages had no intervention. Highly sensitive high-volume quantitative PCR (qPCR)-measured parasitaemia in venous blood samples, and clinical malaria was assessed at baseline and again after six months in both control and MDA intervention villages. The
proportion of the people actually in the village at the time of the survey that received MDA ranged between 93.9% and 97.3% in one village and between 59.6% and 81.3% in the other village. The coverage was much lower when the proportion of the people registered in the census list was considered. Treatment with dihydroartemisinin-piperaquine plus low-dose primaquine was well tolerated. One adverse event was reported for one patient with transient dark urine who had normal G6PD status. After 3 and 6 months, post-intervention results show an important decrease in P. falciparum prevalence to near zero (not in P. vivax), except for a few cases of domestically imported malaria. Data from Cambodia and Viet Nam are currently being gathered.

**Discussion**

Overall, this pilot study showed a considerable asymptomatic reservoir in low transmission settings. The prevalence depends on the sensitivity of the method, which is high with qPCR on a large blood volume (1 ml). Several questions remain unanswered, such as to what extent individuals with very low parasitaemia can transmit P. falciparum, or whether asymptomatic individuals carry the same proportion of resistant parasites. Maintaining high coverage is the major challenge and importation of new cases from outside target areas (vulnerability) may jeopardize the results. Further results are needed before more definite conclusions on the effectiveness of targeted MDA in eliminating falciparum malaria can be made. Improvement of coverage is clearly an issue to be addressed; those not registered or tested and treated could be a reservoir for future infections. The potential for bias in determining baseline prevalence should be considered carefully since the number of people who did not provide a blood sample is unknown and this group might be at higher risk than those who did, as mobile migrant population could be overrepresented among them (hidden reservoir), and on the other hand people who provided a blood sample may have received prior treatment. Serological assessments using pre-erythrocytic or erythrocytic antigens could be considered in evaluating MDA effectiveness.

A wide variety of possible scenarios regarding MDA can be modelled. This will remain important, but at this time the field evaluation of the currently selected scenarios should have priority. There is a rationale for MDA as long as it is not used as an isolated intervention, but is included in a package of quality interventions with the objective of eliminating falciparum malaria. Several questions must be addressed to optimize MDA trials, which include strategies for scaling up, blood volumes and sample sizes for screening and large scale community engagement. MDA remains a high-risk strategy, and the TEG has concerns that it could drive drug resistance further (last man standing). The concern is particularly strong, because the trials are conducted with dihydroartemisinin-piperaquine, which has a high failure rate in Cambodia resulting from resistance to both components. On the other hand it is recognized that there is no other regimen at present with sufficient data on safety and tolerability to be acceptable for MDA. Success depends on coverage achieved. The continued implementation will require an increased participation of national malaria control programmes and timely sharing of information with WHO. Policies for MDA must consider the balance between the need to eliminate and the risk of increasing levels of resistance.

**Recommendations**

More trials examining various aspects of this strategy should be conducted as soon as possible, and these should involve national programmes and WHO for planning and real-time monitoring. At the same time, more studies should be conducted to determine parasite genetic populations in relation to
population movements as well as to define the “reservoir”. The reservoir should include parasites in mosquitoes and possibly infections that were detected but with insufficient DNA to determine the species. In the context of monitoring elimination and defining the “reservoir”, monitoring transmissibility using serology testing in longitudinal studies may be useful.

In principle the treatment used for MDA should be different from the one used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. Whenever possible, rotating the drugs during MDA is desirable. Therefore, it is important to start trials with alternative MDA regimens, primarily to assess safety and tolerability.

7.2 Malaria elimination strategies in the context of artemisinin resistance

Presentation

Among those measures that are specific or particularly relevant to elimination, the prevention of onward transmission is critically important, and will be best achieved if the following conditions are met:

1) Strive for very early detection and treatment, including single primaquine dose for all P. falciparum cases;
2) Implement effective vector control in active transmission foci and keep malaria patients away from Anopheles mosquitoes, e.g. admit cases to hospital and keep in screened wards in non-endemic zone, and ensure use of LLINs in the hospital and after discharge;
3) Identify areas where patients have been since symptoms started;
4) Keep track of individual cases with a national patient register, and;
5) Identify and monitor delays in detection (patient or laboratory driven) and treatment and establish measures to improve timeliness.

The objective of malaria surveillance systems in the elimination phase is to ensure effective detection and treatment of all infections (symptomatic or not). This includes identification of all areas and foci of transmission. In low transmission settings, where people have no malaria immunity, most malaria infections are expected to produce fever; passive case detection should therefore lead to the detection of most malaria infections. However, in the GMS, recent unpublished studies have found high prevalence of asymptomatic carriers in some areas, a phenomenon which is thought to be related to recent reduction of transmission and burden. The continuous presence of health workers is required for good passive case detection in active transmission foci, and is preferable to periodic visits by mobile teams. Active case detection is a complementary strategy.

For elimination programmes, malaria case is defined as: any case in which, regardless of the presence or absence of clinical symptoms, malaria parasites have been confirmed by quality-controlled laboratory diagnosis. Quality of all facilities where malaria is diagnosed and treatment dispensed (pharmacy, non-governmental organizations, clinics, drug vendors) should be closely monitored. All positive cases should be promptly investigated for the purpose of classification, and the planning of adequate interventions in the localities where the infection originated from and where it may have spread. As a rule, case detection is considered effective if the total number of cases reported roughly matches the number of treatments used in the country. Active case detection should be used in populations that may have a high risk of infection to ensure that onward transmission is prevented.
In the elimination phase, the aim is to eliminate malaria in transmission foci. Focus investigations provide the necessary information on populations, vectors and the sites where transmission occurs, and then facilitate the selection of the most appropriate combination of interventions for controlling and eliminating malaria in a specific locality. The inclusion of MDA in an elimination strategy should be carefully planned in terms of timing and methods employed and should be restricted to well-defined areas.

A list of requirements for malaria elimination to be feasible was presented. These requirements include: issues relating to political commitment in the country, the situation of neighboring countries from which malaria may be imported, health regulations, health system infrastructure, financial and human resources. Before embarking on an elimination programme, a feasibility analysis should be carried out and problematic issues should be effectively addressed.

**Discussion**

TEG underlined the need for different approaches for regions, which progress from high endemicity to low endemicity, and those that were always low endemicity areas.

**Recommendations**

A practical plan for the elimination of *P. falciparum* in the GMS should be prepared based on the existing frameworks, which can help steering current initiatives.

### 7.3 Vector control strategies in the context of artemisinin resistance

**Presentation**

An evaluation of repellents as additional method to control residual transmission in malaria pre-elimination settings was presented. The term residual transmission is defined as all forms of transmission that persist despite full, effective coverage with LLINs and/or indoor residual spraying (IRS). Most malaria vector species are not fully susceptible to LLINs and/or IRS because they exhibit one or both sets of the following behavioral traits: 1) insecticide contact avoidance and early-exit behavior that minimize exposure hazards of vectors that preferentially feed indoors on humans, and 2) animal feeding and outdoor-feeding preferences, which are usually mutually associated, minimizing contact with insecticides targeted at the human habitat. Indeed 60% of vector species bite before sleeping time, and many infective bites occur before 22:00 and after 04:00, thus limiting effectiveness of LLINs and IRS. Other vector control methods, such topical repellents, are needed but evidence is lacking, as only few well-controlled trials have been conducted. The Malaria ResT project funded by the Bill & Melinda Gates Foundation was initiated to study the added value of repellents to LLINs for the control/elimination of malaria in Cambodia. This project has three major components:

1. **entomological**: evaluation of the mass effect of repellents on residual malaria transmission, and estimate the individual protective efficacy on wild mosquitoes;
2. **epidemiological**: assess the impact of repellents on the prevalence and incidence of malaria, other parameters important for malaria elimination and arboviroses;
3. **sociological**: assess the acceptability, adherence and adequacy of topical repellents.

The entomological study showed that the tested repellent (KBR3023) exhibits a dose-dependent effect against mosquito bites, providing an 80% protection (5 hours % repellency) from most vector genera and *Anopheles* species. The epidemiological study conducted in the province of Ratanakiri in 2012-2013
showed no impact of the repellent intervention on the prevalence (real-time PCR) of either *P. falciparum* or *P. vivax*. The sociological study showed very low adherence or misuse of repellent but the qualitative component of this study showed high acceptance of the trial and the product. From these preliminary results it is concluded that the lack of impact is due to lack of adherence. Analyses of serology, passive case detection, and per-protocol population data may provide further insight on the usefulness of repellent as part of an elimination strategy. As a collateral benefit, the study has generated an important database to identify hotspots, which are essential for understanding transmission dynamics and targeting control effort. It also identified the need to develop better sampling methods for entomological studies.

**Discussion**

The presence of residual transmission does not mean that distribution and promotion of LLINs should be stopped. On the contrary, it is important to continue implementing this intervention. However, based on good surveillance and geographic progress in interrupting transmission, the target population may be reduced and the efforts more concentrated. If LLINs coverage is adequate, there is in general no added value of IRS, except in specific settings where people are living in housing with sprayable walls, and they are up late at night. The potential of insect growth regulators was discussed and it was agreed that despite the limitations of larval source management in the GMS, this tool might have some potential, as there are several novel methods of applying it.

**Recommendations**

Mosquito nets are already an integral part of national malaria control programmes and must continue to be part of the containment and elimination strategies in the GMS. Personal repellents as programmatic interventions have insufficient evidence but can be an important tool for individual protection. More programmatic efforts should be put into the use of hammock-LLINs. Insect growth regulators should be investigated as a potential malaria vector control tool.

### 7.4 Ivermectin

**Presentations**

*Ivermectin as a malaria elimination tool*

Ivermectin is an endectocide drug that has activity against endoparasites (mainly nematodes) and ectoparasites (killing arthropods that blood-feed on a treated subject). Ivermectin is a macrocyclic lactone isolated from the bacterium *Streptomyces avermitilis*. In invertebrates it acts as a glutamate-gated chloride ion channel agonist, a mode of action that differs from those of insecticides used for LLINs or IRS, and thus could circumvent emerging insecticide resistance.

Ivermectin is one of the few drugs used in MDA campaigns, and more than one billion treatments have been delivered over the last few decades for controlling onchocerciasis, lymphatic filariasis, scabies and other neglected tropical diseases. While ivermectin has no in vitro or in vivo effect on blood-stage *Plasmodium* parasites, it can significantly reduce the survival and/or fecundity of several species of *Anopheles*, including *An. gambiae* s.s., *An. arabiensis*, and *An. stephensi*. Based on in vivo studies and a mosquito age-structured model of malaria transmission, different ways to apply ivermectin in malaria control efforts aimed at reducing transmission were presented and suggested for further investigations. Through current ongoing yearly anti-helminth MDA programmes, it was possible to show that
ivermectin MDA reduced survivorship of *Anopheles*, and suppressed sporozoite transmission for weeks. This effect is temporary and the degree and duration of these reductions must be thoroughly defined before considering repeated MDA as a malaria control intervention. In addition to direct anti-mosquito effects, expected changes in population structures (age grading), and third-order effects on entomological inoculation rate, vectorial capacity, the molecular force of infection and the malaria reproductive rate must be investigated. Current estimates of lethal concentration 50% (LC50) of ivermectin for mosquitoes are based on membrane feeding assays. With simultaneous mosquito feeding and measurement of ivermectin concentration in plasma (capillary and venous blood), it is possible to establish a correlation and to calculate in vivo LC50 and the time post-treatment that the anti-mosquito/anti-sporogenic effect lasts. Additionally, studies have shown that sub-lethal ivermectin concentrations can affect *P. falciparum* transmission by inhibiting sporogony, suggesting that ivermectin MDA may reduce transmission for a longer period. Increasing the use of ivermectin is likely to lead to resistance in other parasites, which would compromise the success of other disease control programmes. Combination therapy with a second anti-helminthic drug, such as albendazole, may be considered. Co-administration of albendazole and ivermectin was shown to be safe in clinical trials. Other studies have shown that albendazole treatment does not interfere with the bioavailability of ivermectin in humans, with its anti-mosquito effect in vitro or in vivo or with its in vitro sporontocidal effect. In the GMS, ivermectin MDA could have a direct effect on exophagic and crepuscular feeding *Anopheles*. Data are available on LC50s for *An. dirus*, *An. minimus*, *An. campestris*, and *An. sawadwongporni*, on re-feeding inhibition of *An. dirus* and *An. minimus*, and on sporontocidal effects on *P. falciparum* and *P. vivax* in *An. dirus* and *An. minimus*. Ivermectin may also be considered with the use of ACT (and primaquine) during MDA to simultaneously eliminate infectious vector and human reservoirs.

*The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission.*

To investigate the potential impact of ivermectin administered at the same time as MDA on malaria transmission, its effect on mosquito mortality was modeled in a three-stage process. Human pharmacokinetic data and mortality data for mosquitoes taking blood meals containing ivermectin were used to quantify the sporontocidal effect of ivermectin. These were incorporated into a transmission model to estimate the impact of ivermectin used in combination with mass treatment strategies with artemether-lumefantrine. Adding ivermectin increases the reductions in parasite prevalence and delays the re-emergence of parasites compared to mass treatment alone. Ivermectin effectiveness depends on coverage, with the highest impact achieved if given to the whole population (all individuals above 5 years; coverage 90%) rather than only to those with detectable parasites. Results also suggest that ivermectin added in a mass treatment strategy can reduce the time taken to interrupt transmission as well as help to achieve transmission interruption in settings in which mass treatment strategies alone would be insufficient. It was also noted that adding ivermectin would not make parasites more resistant. However, mosquitoes could develop resistance to ivermectin. Ivermectin could also be given as MDA independently from an antimalarial drug MDA strategy. These previous results apply only for African settings. When the model was re-parameterized to characterize a “Cambodian-like” transmission setting, assuming 1% prevalence and a seasonality pattern, the impact of ivermectin was much lower. The effect of ivermectin could have been masked by the effect of MDA, which was always included in the
model. It was predicted that since MDA with ACT is likely to have a high impact in a low-prevalence setting, any additional interventions will not add much. However, when a Cambodia-like scenario is re-run without combination with ACT the results show that if ivermectin was to be given as stand-alone, once or twice (in three daily doses at 15 μg/kg) at the start of the rainy season, the impact on malaria incidence would be much more pronounced.

Discussion

Ivermectin is a promising tool, as it does not increase antimalarial drug resistance. MDA intervention with ivermectin and primaquine could possibly protect primaquine from resistance. As ivermectin treatment has no direct benefit related to malaria to the individual taking the drug, ethical issues must be taken into consideration.

Recommendations

The added value of ivermectin when combined with targeted MDA should be investigated. The TEG was encouraged by the widespread and apparently safe and effective use of this drug in MDA campaigns against onchocerciasis in western Africa. Entomological data from areas where ivermectin was deployed and safety data (in terms of highest tolerated doses) should be reviewed prior to MDA trials. Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration. A comparative study of the combinations of ACT plus PQ versus ACT plus ivermectin is planned in Lao PDR. The TEG also recommends other field studies with ivermectin given as MDA, but not necessarily in combination with antimalarial drugs.

7.5 Use of community health/malaria workers and volunteers for improved surveillance and response to support malaria elimination

Presentations

The experience of Cambodia

The role of CHWs for improving surveillance and response to support malaria elimination was assessed and results presented. Both VMWs and CHWs have roles in several key areas of the response to malaria, particularly in the surveillance and information systems, in reaching mobile and migrant populations, or other hard to reach populations, for diagnosis, treatment and behavioral change communication. In Cambodia, tackling malaria in hard to reach villages (i.e. forests in the northeast) was initiated in 2001 by the National Malaria Center supported by the European Union, with a pilot project aimed at providing early diagnosis and treatment. The number of VMWs was increased to include low transmission villages of the northwest in 2009 as part of the artemisinin resistance containment project. With the support of GFATM, other donors, NGOs, and WHO, the VMW programme has been scaled up to about 1600 villages in 17 provinces covering 1 million people from 2001 to 2011 and has now been introduced to support mobile populations. A cross-sectional study employing quantitative and qualitative methods was conducted in 2012 to evaluate the performance of the VMW/mobile malaria worker (MMW) programme. Most indicators were in line with the expected performance target (80%), and some showed higher values. Strengthening the surveillance system will be important in order to reach the elimination goal by 2025. In this context, VMWs shall have a role in the malaria surveillance systems comprising the malaria case information system, day-3 positive alert systems, referral systems, and stock-out alert systems. A description of each system and the potential roles and responsibilities of VMWs in them was presented. The feasibility of surveillance of day-3 positive falciparum cases by
VMWs was tested in pilots. Although significant variations were observed between different partners, the system allowed detecting a day-3 positivity rate of about 21%. VMWs are responsible for a range of tasks including preparing blood slides on day 0, completing forms, administering DOT on days 0-2, obtaining follow-up slides on day 3 and transporting slides and paperwork to their supervising health center. Full engagement of VMWs and adequate financial compensation for specific tasks are needed for the good performance of the day 3 surveillance systems. While staff remuneration, computer literacy, frequent changes in health administrative structures, and mobile networks coverage are some of many challenges to be addressed, VMWs and MMWs have increased the capacity of national programmes and now constitute an essential component of a sustained efforts towards containing resistance and eliminating malaria.

*The experience of Myanmar*

Medical Action Myanmar, an NGO, supports a CHW project in Mon and Kayin States, eastern Myanmar. Villagers were trained to perform rapid diagnostic tests and dispense ACT + primaquine; they were available for patients in their village of residence or other villages nearby at a fixed time. CHWs received a small incentive for each rapid diagnostic test performed. A mobile monitoring team visited each village once a month to assess CHW performance, distribute LLINs, provide health education and obtain feedback of villagers. The CHW project monitoring proved to be expensive (approximately US$ 2000 per village per year), and time-consuming, due to the travel time required between villages. The project started in 2011 and expanded gradually. A retrospective cohort analysis stratified in two 6-month periods (January-June; July-December) was performed and indicated that CHWs were not always available, and that some villages had only few or no cases of malaria. Analysis of the villages with highest initial malaria incidence was presented. In general, falciparum positivity rate decreased in nearly all CHW project villages. In Myanmar, CHW are the only way to reach small remote villages. Success depends on the appropriate selection of CHW to make sure that he/she will be respected by villagers and will not compete with other health providers (e.g. quack), that they have appropriate incentives to maintain their motivation, and have the time to do the tasks in addition to their regular job.

*Discussion*

VMWs, CHWs and MMWs in Cambodia, in Myanmar, and in other countries have a major role in improving surveillance and response to support malaria elimination. VMWs have different mode of operations and conditions according to country. Differences in country context need to be taken into account in the design of CHW or VMW programmes. Countries have expressed concern over the sustainability of altering or creating community health programmes that are dependent on external funding. It was noted that in Viet Nam, 90% of villages have VMWs. It was debated, if resources should be allocated for VMW and CHW to do DOT in the context of elimination.

*Recommendations*

Services provided by CHW or malaria volunteers should be considered an essential element of any malaria control or elimination strategy in GMS. While it is of very high priority to promote good adherence to standard treatment regimens, there is no hard evidence showing a clear benefit of DOT as a public health intervention on adherence at the population level. Therefore, TEG does not recommend a strong emphasis on efforts and funding support for DOT. Investing in research to identify additional methods to improve adherence was considered important. Depending on local conditions and
experience, DOT may be considered in the context of last stages of elimination phase, when there are only a few cases left, and in non-mobile populations.

**7.6 RTS,S/AS01 in low transmission settings for targeted elimination**

**Presentation**

An update on the assessment of the RTS,S/AS01 vaccine and the preparation of policy recommendations was presented. The pathways for WHO RTS,S vaccine policy recommendations include MPAC and the Strategic Advisory Group of Experts (SAGE) on immunization. Following regional consultations, SAGE and MPAC will communicate their specific recommendations to WHO Director General, after which a concept paper will be issued and released to countries for decision-making. The patient enrolment of a phase 3 randomized placebo controlled trial was completed 2011 in 7 African countries. The study included 15 460 children stratified in two age groups, 6-14 weeks old and 5-17 months old, at first immunization. The primary vaccination series consisted of three intramuscular doses given 4 weeks apart. Outcome measures include episode of clinical malaria during 12 months of follow-up in each age category. This multicenter study was conducted in a wide range of malaria transmission intensities (0.01 to 2.0 clinical episodes per child per year). Efficacy was measured in presence of other malaria control interventions: 86% LLINs coverage for infants aged 6 to 12 weeks, and 75% among children aged 5 to 17 months. Final results should be available in the summer of 2014 and will include a follow-up at 30 months in the two age groups, site-specific efficacy, and the effect of a booster dose given 18 months after the third dose.

Available results show no clear variation in efficacy according to transmission level. However, the benefits, in terms of number of episodes prevented, may be highest in high-transmission settings. A 3-fold higher immunogenicity for anti-CS IgG was observed in the older age group. From preliminary results, the assessment indicates that the efficacy is higher among 5-17 month olds than in 6 to 12 week olds. Efficacy wanes substantially by 18 months, and hence the booster dose data will be important for policy assessment. There is an increased frequency of febrile convulsions and meningitis in the vaccine group, compared to the control group, and this warrants further assessments by the Global Advisory Committee on Vaccine Safety. The policy recommendations, to be issued in 2015, will be geographically restricted to sub-Saharan Africa, as no RTS,S data are available from other regions. The EMA filing date is planned for June 2014, and the EMA regulatory decision timing should be Q3 2015, at the earliest.

**Discussion**

In the context of malaria elimination, all age groups would need to be vaccinated. The RTS,S vaccine has not been tested in South-East Asia. In the age groups that were studied, the vaccine shows benefit in terms of lower frequency of clinical episodes; however, to the knowledge of the TEG, its effect on asymptomatic parasitaemia was not studied. A specific concern raised by the TEG was whether RTS,S induced immunity can cause an increase in the asymptomatic but transmissible parasite reservoir. The TEG requested WHO to ask the PATH Malaria Vaccine Initiative and GSK whether data on this and other specific questions are available. The questions and answers are below.

**Recommendations**

Although the TEG has limited expertise on this vaccine, it considers that there is currently insufficient data to suggest a role of the RTS,S vaccine in containment/elimination strategies. The TEG considered it
important to invest in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.

**Post meeting note**

**Questions to PATH Malaria Vaccine Initiative and GSK**

- **a) Do the trials show an impact of RTS,S on submicroscopic parasitaemia?**
  
  No data is available from field trials but the likely answer is yes, from the mechanism of action of RTS,S, which provides 50-60% or more sterile/complete protection in the controlled human malaria infection model.

- **b) Do the trials show an impact in terms of delayed appearance of patent parasitaemia?**
  
  Yes, but limited field pediatric data is available only with AS02. AS01 is better so one can be confident that RTS,S/AS01 will do this.

- **c) Are there data on the impact of submicroscopic gametocytaemia and transmissibility?**
  
  Gametocytaemia is being evaluated in the MAL055 Phase 3 trial; however, subpatent gametocytaemia or transmissibility has not been studied.

- **d) Do the trials show an impact on reducing the genetic diversity of malaria infections?**
  
  Genetic diversity of malaria parasite infections is being evaluated in the MAL055 Phase 3 trial; one hypothesis is that RTS,S vaccination will be associated with reduced genetic diversity by reducing multiplicity of infections in the short term. The long-term effects are less clear.

- **e) What will be the costs of conducting safety studies and efficacy studies in all age groups to enable possible deployment of this vaccine in the Mekong Region?**
  
  This has not been evaluated.

* These answers express the view of PATH Malaria Vaccine Initiative and GSK and were not commented by the TEG.
ANNEX 1: QUESTIONS FROM MPAC FOR THE TEG TO DISCUSS AND GIVE RECOMMENDATIONS ON

1. ARTEMISININ RESISTANCE

a) Should the definition of artemisinin resistance be updated and, if so, in which way?

Yes, with the identification of the mutations in the resistance domains (amino acid positions ≥ 440) of the gene on chromosome 13 encoding for a Kelch protein (K13) as a marker for artemisinin resistance, there was agreement that this definition needed to be updated. However, it was agreed that the clinical phenotype of slow clearance should remain part of the definition. The committee recognizes that the definition might need adaptation as more data become available. As with the previous working definition, a distinction is made between suspected and confirmed artemisinin resistance at a population level. Suspected endemic resistance is defined as a prevalence ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations, or a proportion ≥ 10% of patients still parasitaemic on day 3 by microscopy or ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy. Endemic artemisinin resistance is confirmed when there is a prevalence of ≥ 5% of infections with strains containing Kelch resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy.

b) Does the evidence support the inclusion of provinces in northwestern Myanmar in tier 1?

WHO is awaiting data from clinical studies and molecular analyses from three provinces of Myanmar before issuing formal recommendations. However, the probability of including northwestern provinces of Myanmar in tier 1 is high.

c) How should K13 be used in the surveillance of artemisinin resistance; in particular is an evidence review group on K13 needed (to review available data, reference center, SOPs, data analysis)?

The committee agreed that K13 analysis should be part of all therapeutic efficacy studies on falciparum malaria. However, the science around this new marker is quickly evolving. More than 30 different mutations in the K13 gene have been reported so far, not all of them being located in the propeller domains, and different mutations may confer different resistance phenotypes. Moreover, a set of “permissive” mutations elsewhere in the genome may be a co-factor in emergence of K13-mediated resistance. Given the significance of the discovery and the quickly evolving information, the TEG recommended the establishment of an ERG on the topic to 1) to collect and review data; 2) to indicate which polymorphisms on K13 (and beyond) should have consequences, if detected in a given area, and describe these consequences; this includes a discussion on the development of integrated mapping of the relevant K13 mutations; 3) to propose organizational structures (such as a reference center) that can facilitate standardization of methods and information flow to national programs and WHO; 4) to identify remaining knowledge gaps for research.

d) Which implications does the identification of the K13 mutation have on the response to artemisinin resistance?

The identification of multiple K13 mutations and additional genetic analyses have shown the existence of multiple foci of de novo emergence of artemisinin resistance, in addition to its geographical spread. The “firewall approach” remains an appropriate and necessary containment measure in tier 1 and 2 but additional measures are necessary, which includes an effort for elimination of *P. falciparum* malaria in all affected countries in the GMS where artemisinin resistance has been detected, in addition to intensified measures in sub-Saharan Africa that include improved case detection and treatment of malaria,
uninterrupted supply of essential commodities, scaled up and sustained coverage with vector control measures, intensified efforts to eliminate monotherapy, counterfeit drugs and other substandard treatments, and enhanced therapeutic efficacy monitoring. Evidently, the K13 molecular marker will be an important additional tool for surveillance of artemisinin resistance.

2. Resistance to Other Antimalarial Drugs

a) What are the TEG’s recommendations on the national treatment policies in particular in Thailand and Cambodia?
In Thailand, the first line policy is still artesunate-mefloquine despite the evidence of high failure rate on the border between Thailand and Myanmar and Thailand and Cambodia. The TEG strongly recommends an urgent policy change in Thailand. The TEG will inform MPAC if no policy change is achieved in Thailand by September 2014. For western Cambodia, the TEG supports the implementation of artesunate-mefloquine as a short-term alternative to now failing dihydroartemisinin-piperaquine, but is concerned about the vulnerability of mefloquine. For the time being, it is recommended to use quinine and doxycycline over 7 days as rescue therapy in case of failure with artesunate-mefloquine, while waiting on the results of a study evaluating current efficacy of artesunate-pyronaridine in Western Cambodia. There was no consensus in the committee whether to recommend extension of dihydroartemisinin-piperaquine treatment from a 3 to 5 days course, because of potential safety issues regarding the increased piperaquine dose (QTc prolongation). However, clinical studies (phase I and II) to assess the safety, efficacy, and effectiveness of a 5-day dihydroartemisinin-piperaquine treatment course were recommended to enable an evidence-based recommendation in the near future.

b) What should be the ideal profile of the next generation of antimalarial treatment?
The TEG considered triple combinations of drugs with different modes of actions to be a target product profile for the next generation of antimalarial drugs either using current drugs or by adding a new compound to some of the existing ACTs. The selection of drugs will require appropriate matching of pharmacokinetic profiles (linked to drug potencies) and investigation of potential drug interactions. The absence of new drugs is a major impediment in fighting antimalarial resistance, and TEG expresses desperate needs to accelerate the development of new chemical entities.

c) Should multiple first-line treatments for malaria be promoted as part of the response to resistance?
The evidence examining multiple first-line therapies (MFLT) as a response to resistance is based on two modeling studies only, and those gave contradictory conclusions. In the study which was found to support MFLT, the potential benefit the potential benefit was estimated to relatively minor; likewise the model that did not support MFLT also showed a small effect. Therefore, TEG cannot currently recommend adopting MFLT as a response to resistance but recognizes the need to be flexible and does not oppose such practice, in particular when it is already in place or when used to avoid drug stock outs. The TEG acknowledged that increasing the complexity of treatment policy risks practices that exacerbate rather than mitigate the problem. The potential benefit of doing so seemed insufficient justify recommending it. Measures to ensure drug quality and treatment compliance should be also emphasized.

3. Containment and Elimination - Policy response to antimalarial drug resistance

3.1. Ongoing activities

a) Is regional Plasmodium falciparum malaria elimination a feasible, as opposed to desirable, goal? Consider assumptions, benefits and risks of options and timelines.
The TEG considers malaria elimination to be feasible in the GMS, provided that sufficient funding is available, that the current and new tools are applied correctly, and that good coordination exists between...
donors and implementers. The elimination goal must be translated into concrete action plans, with clear
time lines and responsibilities. A pre-requisite for coordination is a good understanding of the availability
of current and new tools, how these tools are used, and which groups are using them in which
geographical area; this will require an accurate mapping of tools and resources for each targeted region of
artemisinin resistance. Elimination goals and timelines will be set by country and/or regions. The following
preliminary timelines have been proposed:
• Eastern Thailand, Cambodia, Viet Nam, Lao PDR, and China (Yunnan): 2020
• Eastern Myanmar and western Thailand: 2025
• Western Myanmar: 2030

b) If not, what should be the optimal malaria strategy for Greater Mekong subregion (GMS) in a local and
global perspective?
See comments in 4 a)

c) Should WHO work to have artemisinin resistance declared a “Public Health Emergency of International
Concern” (PHEIC)?
The TEG considers that artemisinin resistance does not constitute a PHEIC because the conditions for
PHEIC introduced in the revised International Health Regulations (IHR, 2005)* are not met. As defined in
IHR, a PHEIC is an “extraordinary event” that constitutes an acute public health risk, emphasizing “a
serious and direct danger, to which a sense of urgency can be inferred” and “which may also require a
coordinated response”. IHR were designed to deal with acute (as opposed to chronic) public health
conditions that are readily transmissible and disruptive to international trade. Declaration of a PHEIC by
the WHO has far reaching consequences. While the committee considers artemisinin resistance as serious
and severely threatening public health concern meriting a vigorous and coordinated response, it did not
see it as meeting the criteria for a PHEIC as described above. The emergence of resistance to any class of
drugs is not an “extraordinary event” but one that has occurred time and again with all other classes of
antimalarial drugs over the past 100 years. Although the event is deeply worrying, it does not exceed
reasonable expectations regarding parasite evolution in the face of important selection pressure. The TEG
also recognized that in the context of artemisinin resistance, resistance to ACT partner drugs becomes
equally or more critical than artemisinin resistance per se. The harm being caused by that distinct
problem is not a hypothetical future – it is occurring today in the GMS – often resulting in treatment
failures and illness rather than exhibiting modest delays in cure.

3.2. Mass Drug Administration (MDA)

a) Does the resistance situation in the GMS mean that MDA is no longer rational?
There is a rationale for MDA as long as it is not used as an isolated intervention. MDA could be useful as
part of an elimination strategy if included in the context of a package of interventions, such as a village
health worker program for early diagnosis and treatment and, where appropriate, mosquito net
distribution. However, a key problem is the lack of evidence to guide optimizing the approach in any given
setting. Initial analysis of a pilot study using targeted MDA (3 rounds of a monthly full course of
dihydroartemisinin-piperaquine) in villages with high malaria prevalence, show the expected results in
reducing prevalent *P. falciparum*, but (as expected due to the untreated hypnozoite reservoir in the
community) less so for *P. vivax*. Although not measured in that pilot work, success with MDA almost
certainly depends on the coverage achieved, i.e. the proportion of people receiving therapy. The people
most likely to be missed in MDA may also be the most likely to later reintroduce parasites into their

communities, i.e. mobile and migrant populations, or those frequenting the forest. This potential pitfall implies that a sufficiently large area has to be covered when implemented. Several questions must be addressed to optimize targeted MDA trials, which include strategies for scaling up (such as blood volumes and sample sizes for screening, large scale community engagement and acceptance and support). MDA remains a high-risk strategy, since it has the potential to increase drug pressure on the parasite population driving increasing drug resistance (last man standing), so that efforts need to be maintained until elimination has been achieved. Until recently, opposition from countries has delayed the implementation of targeted MDA trials. The TEG recommends that more trials looking at various aspects of this strategy should be conducted as soon as possible and that national programmes and WHO should be involved in planning and evaluation with real-time sharing of information. Currently small-scale projects are being conducted or planned in Cambodia, in Myanmar near the border with Thailand, and in Viet Nam. Another study could be conducted in Bangladesh near the border with Myanmar, if funding is granted.

b) If no, where does MDA have a role (socio-economic situations, epidemiological settings and resistance tiers)?
   Not addressed.

c) Which drugs should be used in MDA?
   As a basic principle, the drug used for MDA intervention should be different from those used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. When possible, rotating the drugs used for MDA is recommended. The recommendation for targeted MDA is a balance between the need to eliminate *falciparum* malaria in an area with artemisinin resistance, and the risk of increasing drug resistance potentially losing the drug to full resistance. However, if MDA achieves permanent elimination, the antimalarial drug where applied will no longer be needed, and of course all of the parasites expose to the applied drug are, in principle, dead and gone.

d) Are there other interventions with which MDA should be combined in a fixed way? If yes, which should be prioritized immediately in operations or in research?
   MDA is already part of a package of interventions. Research on how to include ivermectin in MDA should be prioritized.

e) How should MDA be planned and monitored?
   Real-time data should be available, and WHO should be involved in planning and evaluation.

f) What further inputs are needed from geneticists and modelers on MDA?
   A wide variety of possible scenarios regarding MDA can be modeled, but there are few real world data to inform the models or verify output. This will remain important, but at this time the field evaluation of the currently selected scenarios should have priority. The TEG acknowledges the need for more research on parasite population genetics in relation to population movement as well as research on a better understanding of the sub-patent parasite reservoir. In the context of monitoring elimination and defining the reservoir, monitoring transmissibility using serology testing in longitudinal studies may be useful in addition to the currently used genetic methods.

3.3. **VECTOR CONTROL**

a) Which role should vector control interventions including ivermectin play in elimination/containment/control strategies in the GMS, considering effect, cost-effectiveness and alternative uses of the resources?
Mosquito nets should be part of the containment activities and are already an integral part of national malaria control programmes with high population coverage in many regions. Personal repellents as programmatic interventions have shown very limited impact, but can be important for individual protection. The choice of vector control interventions should be informed by understanding of both mosquito and human behaviors. Regarding ivermectin, research to investigate the added value of this vector control tool when combined with targeted MDA is recommended. Prior to larger studies involving ivermectin, entomological data from areas where ivermectin was deployed can be insightful. Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration. A comparative study of the combinations of ACT plus primaquine versus ACT plus ivermectin is planned in Lao PDR. The TEG encourages implementation of other field studies with ivermectin. Research on other vector control methods to address residual transmission is also a priority.

3.4. ADDITIONAL TOOLS FOR MALARIA ELIMINATION

a) What is the role of classical elimination tools such as focus-based interventions and active case detection in the context of artemisinin resistance in GMS?

These tools are relevant, but need to be assessed and adapted to the epidemiological and operational realities of each country. However, the assessments that have been done offer little encouragement. The diagnostics technology that would enable such an approach is simply not available; the simple and quick methods are far too insensitive, and the complex and slow methods are more sensitive but, in any event, too expensive for consideration by NMCPs.

b) What is the role of vaccination against malaria, especially RTS,S in the containment/elimination strategies?

Although the TEG has limited expertise on this vaccine, it considers that there is currently insufficient data to suggest a role of the RTS,S vaccine in containment/elimination strategies. RTS,S was designed to prevent severe morbidity and mortality rather than infection per se. A specific concern raised by the TEG was whether RTS,S induced immunity can cause an increase in the asymptomatic but transmissible parasite reservoir. The TEG considered it important investing in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.

c) Is there any role for financial incentives to seek proper treatment in any areas?

The TEG believes financial incentives for seeking proper treatments is ethically dubious and socially not sustainable.

d) To which extent should funding be spent on implementation of directly observed treatments (DOTs) and follow-ups?

Based on effectiveness studies and the tuberculosis experience there is no hard evidence showing a clear benefit of DOT as a public health intervention on treatment compliance at the population level. Therefore, TEG does not recommend more funding to support DOT. Investing in research to identify additional methods to improve adherence was considered important. DOT may be considered in the context of last stages of elimination phase when there are only a few cases left and in non-mobile populations. In other words, where there are many cases, DOT bears very high costs and little reward; but where cases are few DOT bears few costs and enormous reward.

e) What actions, if any, should be recommended for groups such travelers and military entering or leaving areas with artemisinin resistance?

This topic was addressed only partially but will be included on the agenda of the next TEG. It was agreed that military should be treated for preventing importation or exportation of resistant parasites in the GMS. Specific actions will be needed for UN. The TEG will review a set of recommendations for the UN through
email. Recommendations to travelers should be issued by the TEG on Chemotherapy in concert with the WHO division of International Travelers and Health. A regional meeting addressing the issues of malaria control in the military in the context of artemisinin resistance, organized by donors, WHO ERAR hub and the RSC RAI, will take place in Viet Nam 19-20 June.

f) **Does the TEG recommend the use of standby treatment for mobile populations?**

Under exceptional circumstances, when there are no malaria workers or health services, the TEG considers standby treatment for mobile populations acceptable provided the treatment is a quality-assured ACT. Drug should be provided as part of a kit containing nets and diagnostic tool(s). However, mobile malaria workers are a better solution and experience with them is accumulating.

g) **What other tools should be emphasized in the drive toward malaria elimination?**

Not addressed.

4. **SUMMARY AND IMMEDIATE NEXT STEPS**

a) **Since the development of the Global Plan for Artemisinin Resistance Containment (GPARC), research has provided additional information on artemisinin resistance, and resistance has been identified outside the area on the Cambodia-Thailand border. Is it now possible to identify a strategy for containment of artemisinin resistance i.e. to prevent or significantly and verifiably delay its spread beyond GMS biogeographic region or eliminate artemisinin resistant parasites?**

The area within the GMS affected by artemisinin resistance appears to have expanded significantly over the last few years. Genetic studies indicate that this is partially due to geographic spread but also de novo emergence of resistant mutants. It must thus be acknowledged, therefore that containment based only the “firewall principle” (preventing spread from a persistent focus) will unlikely be effective on its own. However, artemisinin resistance with clinical relevance is still confined to a relatively limited area of continental South-East Asia. Prevention of spread of artemisinin resistant falciparum malaria remains important, especially because the same strains are increasingly also resistant against the main partner drugs (lumefantrine, mefloquine, piperaquine) as well as atovaquone-proguanil. From a global perspective, there is therefore now a strong case for prioritizing falciparum malaria elimination in the GMS countries, in addition to the “firewall approach”. Achieving this objective within a limited time could delay the emergence of multidrug resistance in other parts of the world, probably until or after new effective, safe and affordable antimalarial drugs become available. An additional argument is that, if falciparum malaria persists in the GMS countries, this subregion will be the first to need novel antimalarial drugs and will therefore again be the source of multidrug resistance to affect global control and elimination efforts.

However, malaria elimination in the GMS countries is severely hampered exactly by the widespread drug resistance. As in the past, this converges with highly exophilic vectors and extensive population movement. But there are also several factors that will facilitate falciparum elimination in this region: the vectorial capacity even in forest environments is not very high in this part of the world, meaning that interventions which can circumvent the outdoor transmission are likely to be highly effective; health systems are rapidly becoming stronger, as economies grow. In fact, the malaria burden has been greatly reduced in these countries over the last 20 years. Furthermore, national malaria control programmes now have at their disposal an array of interventions and information technologies, which were not known only a few decades ago. Although it is not possible at present to identify a definite, uniform strategy, which is guaranteed to lead to elimination within a few years, the TEG considers it likely that continued, fully scaled-up and improved implementation of the current standard interventions supplemented by
novel interventions specifically aiming at elimination, which are ready or almost ready to be validated through field research can lead to elimination of falciparum malaria in the GMS countries. 

The assessment that time-limited elimination is feasible is based on the following assumptions:

1) that the effort is fully and continuously funded across the subregion until the objective has been achieved;
2) that there is continued excellent collaboration and coordination between countries, between countries and partners, between researchers and national malaria control programme managers and between partners;
3) that the remaining focal security problems will be solved rapidly and that no serious armed conflicts will emerge.

Progress in elimination of falciparum malaria in these countries will to a large extent serve as pathfinder for vivax malaria elimination. New tools are likely to become available for vivax malaria elimination within the next few years. Thus, vivax malaria elimination is likely to be achievable only a few years after falciparum malaria elimination in these countries. It is likely that a malaria elimination agenda, having more tangible objectives, will be more strongly supported by national and local governments as well as affected communities than containment plans have been in the past.

b) If not, what is the TEGs role in ensuring that consensus is achieved and how should that role be fulfilled?
   Not addressed.

c) What should the MPAC do to support the TEG further in its work?
   The TEG has recommended elimination of falciparum malaria in the GMS. With the support of a consultant, a subgroup of the TEG will prepare an analysis of the feasibility of malaria elimination in GMS, an estimation of the potential costs, and outline an elimination plan. This will be complemented by more detailed operational planning by the ERAR hub. As a matter of urgency, MPAC is requested to review this analytical work and provide any additional inputs. If MPAC deems elimination in GMS feasible with the proposed timelines from technical and financial viewpoints, it is requested to lend the proposed outline plan of action its full support, and then maintaining the political and financial momentum.
TECHNICAL EXPERT GROUP ON DRUG RESISTANCE AND CONTAINMENT

28-30 APRIL 2014, STARLING 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 (unable to attend)
University of Cape Town
Cape Town, SOUTH AFRICA

Marc COOSEMANS (invited speaker)
Institute of Tropical Medicine
Antwerp, BELGIUM

Lesong CONTEH
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 (unable to attend)
National Malaria Control Programme
Kigali, RWANDA
Kevin KOBYLINKSI (invited speaker)  
Armed Forces Research Institute of Medical Sciences  
Bangkok, THAILAND

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

Hannah SLATER (invited speaker)  
Imperial College  
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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 Malaria, Parasitology and Entomology  
Hanoi, VIET-NAM

Stephen VREDEK  
Academic Hospital Paramaribo  
Paramaribo, SURINAME
OBSERVERS

Stephan DUPARC
Medicines for Malaria Venture
Geneva, SWITZERLAND

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

Sandrine Lourenço
The Global Fund to Fight AIDS, Tuberculosis and Malaria
Geneva, SWITZERLAND

Izaskun GAVIRIA
The Global Fund to Fight AIDS, Tuberculosis and Malaria
Geneva, SWITZERLAND

Jillian JOHNSTON
Department for International Development
London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Tom KANYOK
The Bill and Melinda Gates Foundation
Seattle, UNITED STATES OF AMERICA

Wiweka KASZUBSKA
Medicines for Malaria Venture
Geneva, SWITZERLAND

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

Micheal O’DWYER
Australian Department of Foreign Affairs and Trade
Bangkok, THAILAND

Meera VENKATESAN
USAID/PMI
Washington, UNITED STATES OF AMERICA
WHO SECRETARIAT

Global Malaria Programme

Amy BARRETTE
Technical Officer
Drug Resistance and Containment Unit, GMP

Andrea BOSMAN
Coordinator
Diagnostic, Treatment and Vaccine, GMP

Alison OSBORNE
Team Assistant
Drug Resistance and Containment Unit, GMP

Carmem Lúcia PESSOA-SILVA
Medical officer
AMR, Infection Control and Publications Unit, PED

Charlotte RASMUSSEN
Technical Officer
Drug Resistance and Containment Unit, GMP

John REEDER
Director a.i.
Global Malaria Programme

Aafje RIETVELD
Medical officer
Surveillance, Economic and Elimination Unit, GMP

Pascal RINGWALD
Coordinator
Drug Resistance and Containment Unit, GMP

Lise RIOPEL
Consultant
Drug Resistance and Containment Unit, GMP

Marian WARSAME
Medical Officer
Drug Resistance and Containment Unit, GMP
# TECHNICAL EXPERT GROUP ON DRUG RESISTANCE AND CONTAINMENT

**28-30 April 2014 – Starling hotel, Geneva, Switzerland**

## Monday 28 April 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00–09:15</td>
<td>Welcome</td>
</tr>
<tr>
<td></td>
<td>J. Reeder – ai Director GMP</td>
</tr>
<tr>
<td></td>
<td>A. Dondorp – Chair TEG DRC</td>
</tr>
<tr>
<td>09:15–09:30</td>
<td>Declaration of interest, agenda, Global Technical Strategy</td>
</tr>
<tr>
<td></td>
<td>P. Ringwald</td>
</tr>
<tr>
<td>09:30–10:00</td>
<td>Minutes and action points last meeting</td>
</tr>
<tr>
<td></td>
<td>A. Dondorp</td>
</tr>
</tbody>
</table>

**Session 1: Update on drug resistance**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:00–10:40</td>
<td>i) TRAC studies</td>
</tr>
<tr>
<td></td>
<td>A. Dondorp</td>
</tr>
<tr>
<td>10:40–11:00</td>
<td>Coffee/tea break</td>
</tr>
<tr>
<td>11:00–12:30</td>
<td>ii) Artemisin resistance confirmatory study in Suriname</td>
</tr>
<tr>
<td></td>
<td>S. Vreden</td>
</tr>
<tr>
<td></td>
<td>iii) Policy change in Cambodia</td>
</tr>
<tr>
<td></td>
<td>S. Sovannaroth</td>
</tr>
<tr>
<td>12:30–13:30</td>
<td>Lunch</td>
</tr>
<tr>
<td>Time</td>
<td>Session/Activity</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 13:30–15:30     | iv) Update on K13 molecular marker  
C. Plowe  
v) Update on artemisinin resistance definition and tier maps  
P. Ringwald | → For information and decision                                           |
| 15.30-16.00     | Coffe/tea break                                                                  |                                          |
| 16:00–18:00     | **Session 2: Modelling**                                                          |                                          |
|                  | i) Impact of spread of artemisinin resistance to Africa  
H. Slater invited speaker  
ii) Multiple first-line treatments: outcome of recent modelling efforts  
I. Hastings  
iii) The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission  
H. Slater invited speaker | → For information and decision                                           |
| 18:30–20:00     | Reception                                                                        |                                          |
| **Tuesday 29 April 2014** |                                                                                     |                                          |
| 09:00–10:30     | **Session 3: Update on recent containment and elimination efforts**                |                                          |
|                  | i) Emergency Response to Artemisinin Resistance (ERAR) project in the Greater Mekong subregion  
C. Rasmussen  
ii) Update on the Regional Artemisinin resistance Initiative (RAI)  
S. Filler | → For information                                           |
<p>| 10:30–11:00     | Coffe/tea break                                                                  |                                          |
| <strong>Session 4: Elimination of artemisinin resistance in the GMS</strong> |                                          |                                          |</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:00–12:30</td>
<td>i) MDA pilot studies in the GMS&lt;br&gt;<strong>A. Dondorp</strong>&lt;br&gt;ii) Malaria elimination strategies in the context of artemisinin resistance&lt;br&gt;<strong>A. Rietveld</strong></td>
<td>→ For information and decision</td>
<td></td>
</tr>
<tr>
<td>12:30–13:30</td>
<td>Lunch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13:30–15:00</td>
<td>iii) Vector control strategies for malaria elimination in the context of artemisinin resistance&lt;br&gt;<strong>M. Coosemans invited speaker</strong>&lt;br&gt;iv) Ivermectin as an malaria elimination tool&lt;br&gt;<strong>K. Kobyliński invited speaker</strong></td>
<td>→ For information and decision</td>
<td></td>
</tr>
<tr>
<td>15:00–15:30</td>
<td>Coffee/tea break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:30–17:00</td>
<td>v) Use of community health workers (CHWs) and other volunteers for improved surveillance and response to support malaria elimination:&lt;br&gt;- the experience of Cambodia: <strong>S. Meek</strong>&lt;br&gt;- the experience of Myanmar: <strong>F. Smithuis</strong></td>
<td>→ For information and decision</td>
<td></td>
</tr>
<tr>
<td>17:00–17:30</td>
<td>vi) RTS,S/AS01 in low transmission settings for targeted elimination&lt;br&gt;<strong>A. Bosman</strong></td>
<td>→ For information and decision</td>
<td></td>
</tr>
</tbody>
</table>

**Wednesday 30 April 2014**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00–10:30</td>
<td>Formulation of TEG recommendations&lt;br&gt;<strong>A. Dondorp</strong></td>
<td></td>
<td>Closed session</td>
</tr>
<tr>
<td>10:00–10:30</td>
<td>Coffee break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:30–12:00</td>
<td>Adoption of TEG recommendations&lt;br&gt;<strong>A. Dondorp</strong></td>
<td></td>
<td>Closed session</td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>12:30</td>
<td>Closing remarks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. Dondorp/P. Ringwald</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:30–13:30</td>
<td>Lunch</td>
<td>Closed session</td>
<td></td>
</tr>
</tbody>
</table>