Summary and recommendations

Arjen Dondorp, on behalf of the Technical Expert Group for Drug Resistance and Containment
Session 1: Update on drug resistance - surveillance

- Tracking Resistance to Artemisinin Collaboration studies
- Artemisinin resistance confirmatory study in Suriname
- Antimalarial treatment policy change in Cambodia
- Update on K13 molecular markers
- Update on artemisinin resistance definition and tier maps
TRAC: Heat-map Artemisinin resistance

Admission prst >10,000/µL; <200,000/µL
3 days artesunate followed by ACT-course

Ashley et al.
K13 SNPs are associated with delayed parasite clearance

Ariey et al. Nature 2013
TRAC genotype-phenotype association

*K13* mutation > 441
*K13* wild type or mutation < 441
Unknown

*Ashley et al. N Engl J Med 2014*
Genotype – phenotype associations (24 mutations in the propeller region of Kelch 13)

F446I common in Yunnan province (34%, N=400)
Significantly associated with day 3 positivity
Huang et al. unpublished
Kelch 13 in Africa

Q613E; A578S; A557S; S522C

V589I; A578S; E509V

"Pooled" genotyping
A557S at 36.3% in DRC
R471R at 9.8% in DRC
V581V at 7.1% in Bas-Congo
V520A at 13 sites
(frequency 1.3% - 3.3%)

## Artemisinin resistance in South America?

- *Fr. Guyana; Guyana; Suriname*

<table>
<thead>
<tr>
<th></th>
<th>Coartem 2005/06</th>
<th>Coartem 2011</th>
<th>Artesunate 2013/14 (33 pts.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 2</strong></td>
<td>18 %</td>
<td>75 %</td>
<td>60.6 % (20 pts.)</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td>2 %</td>
<td>31 %</td>
<td>9.1 % (3 pts.)</td>
</tr>
</tbody>
</table>

K13 genotyping: pending  
Slope analysis: pending

*Courtesy Dr Stephan Vreden*
Conclusions (1)

- Artemisinin resistance is both spreading and emerging independently
  - Fire-wall strategy alone is not sufficient: Pf elimination in affected areas; Prevention of emergence: good quality drugs, no monotherapy etc.
  - However, prevention of spread of resistance from GMS, remains crucial, also because falciparum malaria is become increasingly resistant to the main new partner drugs (lumefantrine, mefloquine, piperaquine).
  - Adaptation of Tier map..
- K13 propeller region SNPs are closely associated with delayed parasite clearance in Cambodia, Vietnam, Thailand, Myanmar and China (and Laos)
- No convincing evidence that the slow clearance artemisinin resistant P. falciparum phenotype has reached Africa or South America
  - But: K13 propeller region mutations are present in low frequencies
  - Do other polymorphisms “permit”, modulate or compensate for K13 effects?
  - Certain SNPs associated with higher level resistance (as with DHFR, DHPS)?
Definition of artemisinin resistance

• Current working definition (GPARC document):
  – an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
  – a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance)
Some guiding principles for a new definition

- It should be practical to use in the field.
- It should include both the clinical phenotype and genotype (since still remaining questions around K13).
- It should be sensitive to detect new foci, but on the other hand not raise the alarm unnecessarily all the time.
- A distinction is made between suspected and confirmed artemisinin resistance at a population level.
- It will acknowledge that refinement of the definition is likely with more data becoming available.
- It should clearly distinguish between artemisinin resistance and ACT failure/resistance to both components.
Parasite half life c580y vs wild type Kelch 13

Ashley et al.
Submitted
New definition of artemisinin resistance

- Suspected artemisinin resistance:
  - ≥ 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
New definition of artemisinin resistance

- **Confirmed artemisinin resistance:**
  - prevalence of ≥ 5% of infections with strains containing Kelch 13 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
New definition of artemisinin resistance

- Caveats
  - Clearance is faster with ACTs than with AS monotherapy
  - There are many potential confounders:
    - Drug quality sub-therapeutic drug concentrations
    - Immunity
    - Splenic function/splenectomy
    - Others
  - K13/ genetic epidemiology evidence still rapidly evolving
  - Definition could thus change over time
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.

Beware of confounding factors affecting efficacy (such as drug quality).
Decision making for TES studies

Day 3: % patients parasitemic

- < 10%
  - Response: No change in treatment policy required
  - Interpretation: No evidence of resistance to artemisinin
  - Partner drug is effective

- ≥ 10%
  - Response: Confirm resistance to artemisinin
  - Interpretation: No change in treatment policy required
  - Partner drug is failing

- ≥ 10% or < 10% but increasing over time
  - Response: Change ACT
  - Interpretation: Suspected resistance to artemisinin
  - Partner drug is failing

Day 28 or 42: % treatment failures

- < 10%
  - Response: No change in treatment policy required
  - Interpretation: No evidence of resistance to artemisinin
  - Partner drug is effective

- ≥ 10%
  - Response: Confirm resistance to artemisinin
  - Interpretation: No change in treatment policy required
  - Partner drug is failing

*Day 3 parasite density interpretation to include an evaluation of:
  - baseline parasitemia
  - host immunity
  - trends over time
New Tier map: whole Myanmar Tier 1 or 2
(to be adopted by countries)

24% F446I
1% P553L
1% P574L
1% A676D

10% F446I
3% R561H
7% P574L

54% C580Y
23% R539T
23% wild type
Corresponding MPAC questions

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

See above

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. For now the TEG recommends that whole Myanmar outside the Tier 1 areas should be denoted Tier 2, and that 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.
How should K13 be used in the surveillance of artemisinin resistance; in particular is an evidence review group on K13 needed?

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 ‘backbone’ mutations, or partner drug associated mutations) 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.
Which implications does the identification of the K13 mutation have on the response to artemisinin resistance?

There is ‘spreading and popping’. The “firewall approach” remains necessary for tier 1 and 2 areas 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.
Session 1: Update on drug resistance - continued

-Antimalarial treatment policy change in Cambodia
ACT (and other) 42-D failure rates

DHP (2013) 40%
DHP (2013) 15%
DHP (2013) 0%
DHP (2010) 21%
AM (2012) 0%
AP (2013) 30%
DHP (2012) 19-31%
DHP (2012) 32%
DHP (2012) 0%
DHP (2012) 0%
DHP (2012) 0%
AM (2008) 19%

Sources: CNM Cambodia, WHO, PubMed
<table>
<thead>
<tr>
<th>Location of study site</th>
<th>Treatment</th>
<th>Treatment duration (days)</th>
<th>N</th>
<th>N recurrences</th>
<th>Efficacy % (95% CI) without PCR correction</th>
<th>Efficacy % (95% CI) with PCR correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pailin</td>
<td>AS4 + DP</td>
<td>6</td>
<td>100</td>
<td>2</td>
<td>97.7 (90.9-99.4)</td>
<td>97.7 (90.9-99.4)</td>
</tr>
<tr>
<td>Binh Phuoc</td>
<td>AS2 + DP</td>
<td>6</td>
<td>60</td>
<td>0</td>
<td>100 (93.2-100)</td>
<td>100 (93.2-100)</td>
</tr>
<tr>
<td>Binh Phuoc</td>
<td>AS4 + DP</td>
<td>6</td>
<td>60</td>
<td>0</td>
<td>100 (93.0-100)</td>
<td>100 (93.0-100)</td>
</tr>
<tr>
<td>Attapeu</td>
<td>AS4 + AL</td>
<td>6</td>
<td>60</td>
<td>1</td>
<td>98.2 (88.0-99.8)</td>
<td>100 (93.5-100)</td>
</tr>
<tr>
<td>Attapeu</td>
<td>AS2 + AL</td>
<td>6</td>
<td>60</td>
<td>2</td>
<td>96.6 (86.9-99.1)</td>
<td>100 (93.6-100)</td>
</tr>
<tr>
<td>Shwe Kyin</td>
<td>AS4 + AL</td>
<td>6</td>
<td>40</td>
<td>0</td>
<td>100 (87.9-100)</td>
<td>100 (87.9-100)</td>
</tr>
</tbody>
</table>

But high efficacy with 3 day AS followed by ACT
**Corresponding MPAC question**

What are the TEG’s recommendations on the national treatment policies in particular in Thailand and Cambodia?

- In Thailand, despite high failure rates the first line policy is still MAS3. 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 MAS3 (fixed combination) as a short-term alternative to now failing DHA-PPQ, but is concerned about the vulnerability of mefloquine (PfMDR1 amplification is acquired quickly). Quinine with doxycycline over 7 days is recommended as rescue therapy in case of failure with artesunate-mefloquine. A study on artesunate-pyronaridine in Western Cambodia is ongoing and if still efficacious will be recommended. There was no consensus whether to recommend extension of dihydroartemisinin-piperaquine treatment from a 3 to 5 days course, because of potential safety issues (QTc prolongation). However, urgent safety, efficacy and effectiveness studies of the 5-day DHA-PPQ regimen was recommended by the TEG.
Session 2: Modeling

Impact of spread of artemisinin resistance in Africa *(shows the importance of concomitant partner drug resistance on increase in incidence, prevalence, mortality in the African context; slides on request)*

Multiple first-line treatments: outcome of recent modeling efforts
Forcing the parasite to experience a diverse set of drugs in a short time makes drug resistance evolution difficult for the parasite.

Different colored circles are different drugs (different molecules).

Different colored circles are individuals treated with different drugs or therapies.
## Comparison

<table>
<thead>
<tr>
<th>Population Biology Methods</th>
<th>Population Genetic Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Track absolute population sizes, so we always know how many infected individuals there are.</td>
<td>Do not track absolute population sizes, thus we do not know how many infected individual there are at any point in time.</td>
</tr>
<tr>
<td>Can explicitly track gene frequencies (pop-bio papers on previous slide do track gene frequencies).</td>
<td>Explicitly track gene frequencies.</td>
</tr>
<tr>
<td>Do not assume a fixed multiplicity of infection.</td>
<td>Assume fixed multiplicity of infection, but these epidemiological features change during the course of a treatment strategy.</td>
</tr>
<tr>
<td>Explicitly track the <strong>absolute number of treatment failures (NTF)</strong> in the population that result from drug resistance.</td>
<td>Cannot track the absolute number of treatment failures because changes in malaria prevalence are not tracked over time.</td>
</tr>
</tbody>
</table>

\[
\text{NTF} = \text{total number of people not receiving treatment} + \text{total number of people receiving treatment but experiencing early/late treatment failure}
\]

We want to choose a drug deployment policy that minimizes NTF.
Comparisons Using the Individual-Based Model

Each black circle represents the output of one stochastic individual-based simulation.

100 simulations were run for each strategy.

Red lines are inter-quartile ranges across the 100 simulation runs.

Population size is 1 million individuals in these simulations.

**Cycling**: a single drug is used for 5 years, after which it is replaced with a different drug, and so on. The cycling period is fixed at 5 years.

**Adaptive Cycling**: a single drug is used until the population experiences 10% treatment failure, at which point the drug is replaced, and so on.

**Multiple First-line Therapies**: three drugs are deployed simultaneously, with each individual having an equal probability of receiving a particular drug.

Boni et al 2008, PNAS 105:14216
The basics: Sequential drug deployment

Next drug

+ untreated

+ untreated

---

Frequency

---

No net change in ‘blue’ resistance

The basics: MFT drug deployment

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Frequency

Hitchhiking

Multidrug resistant

No recombinational loss in treated individuals

How big is the effect??

“for 75.1% of the parameter combinations, MFT outperformed a cycling policy”

Number treatment failures:

- 64.4% policies within 5% of each other
- 20.9%........ MFT 5-10% better
- 9.5%.......... MFT >10% better
- 3.6%........... MFT 5-10% worse
- 1.6%.............MFT >10% worse

Boni et al 2008, PNAS 105:14216
Boni et al conclude MFT slightly better (~10%) overall. Hastings et al think it is slightly worse (~5%) at high drug coverage.

→*Given the size of these effects MFT unlikely to be a “game changer”*
Corresponding MPAC question

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. 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.
Session 3:
Update on recent containment and elimination efforts
- ERAR
- RAI
- Multi-donor trust fund (secretariat: ADB)
Organogram – ERAR specific staff

Staff providing regional support

Regional hub, Cambodia
- Coordinator, Emergency response to art. resistance
- Technical officer, M&E
- Technical officer, Adv. & communication
- Assistant

WHO China
- Medical officer, Communicable diseases
- National officer, Malaria

WHO Laos
- Malaria medical officer

WHO Viet Nam
- Malaria medical officer
- National officer, Malaria
- National officer, Malaria

WHO Cambodia
- Malaria Medical officer
- Medical officer, M&E
- National officer, Malaria

WHO Thailand
- Technical officer, Migrant & Mobile populations
- Technical officer, TES

WPRO, Manila
- Medical officer, TES and research

WHO GMP, Geneva
- Technical officer, Pharmaceuticals
- Technical officer, Reporting and surveillance
- National officer, Containment activities

Staff providing country specific support

WHO China
- National officer, Malaria

WHO Laotian
- National officer, Malaria

WHO Viet Nam
- National Officer, Malaria
- National Officer, M&E
- National Officer, MARC

WHO Cambodia
- National officer, Malaria
Regional Artemisinin Initiative (RAI)

**WHO HUB**
- Policy advice/TA to RSC, CCM, RAI PR and SRs/M&E

**RSC**
- Policy development and oversight of overall implementation

**5 CCMs**
- Policy development as members of RSC and oversight of in-country implementation

**GFATM**
- Grant management

**RAI PR (UNOPS)**
- Implementation

**LFA**
- Verification of implementation and reports to GFATM

**Co-PRs & SRs**
- Implementation
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.
Corresponding MPAC questions

Is regional Plasmodium falciparum malaria elimination a feasible, as opposed to desirable, goal?

See feasibility report (next session)

Should WHO work to have artemisinin resistance declared a “Public Health Emergency of International Concern” (PHEIC)?

WHO stated that the conditions for PHEIC outlined in the revised International Health Regulations (2005) are not met. Declaring an PHEIC has far reaching consequences, which we considered not appropriate for the response to artemisinin resistance.
Session 4: Elimination of artemisinin resistance in the Greater Mekong subregion

-Mass drug administration pilot studies in the Greater Mekong subregion
-Malaria elimination strategies in the context of artemisinin resistance
-Vector control strategies in the context of artemisinin resistance
-Ivermectin
-Use of community health/malaria workers and volunteers for improved surveillance and response to support malaria elimination
-RTS,S/AS01 in low transmission settings for targeted elimination
TME targeting the asymptomatic parasite reservoir

Effects of different sensitivities of detection on estimated prevalence of malaria

- RDT
- Microscopy
- Small volume PCR
- Large volume PCR

Alive? Transmissible? Resistance?

Malaria

- 100,000/mL
- 50,000/mL
- 1,000/mL
- 100/mL
- 10/mL
Parasitaemias Pailin compared to Thai-Myanmar border

![Graph showing parasitaemia levels in microL (qPCR estimate) with microscopy detection threshold]

**Graph Details:**
- **Y-axis:** Parasitaemia/µL (qPCR estimate)
- **X-axis:** Cambodia and Thai-Burmese border areas
- **Threshold:** Microscopy detection threshold

**Legend:**
- Black dots represent data points
- Red area indicates the microscopy detection threshold
Do nothing [grey]
Scale up of VMW and ITN in all villages within 10 km of Chey Saen [green]
TME three rounds separated by 1 month in Q3 of 2014 no scale-up [Cyan]
TME three rounds separated by 1 month in Q3 of 2014 with scale up of VMW and ITN in all villages within 10 km of Chey Saen [blue]
Preliminary conclusions

- Asymptomatic reservoir considerable, even in low transmission setting

Targeted malaria elimination with 3 rounds of DHA-PQP and low dose PQ:

- Well tolerated
- Seems effective in eliminating the P.f. reservoir
  But less effective for P.v.
- Maintenance of high coverage is a challenge
- Import of new cases from outside is a vulnerability

Data from Cambodia and Viet Nam to follow
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.
Corresponding MPAC questions

Does the resistance situation in the GMS mean that MDA is no longer rational?

Which drugs should be used in MDA?

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?

How should MDA be planned and monitored?

Does the TEG recommend an evidence review group on MDA?

What further inputs are needed from geneticists and modelers on MDA?
Most malaria vectors in the GMS are outdoor-feeding (exophagic), outdoor-resting (exophilic) or feed before bedtime (crepuscular), and much of the malaria transmission occurs in forested areas during work, not in the village home.

Therefore we need vector control measures that account for human and vector behavior!

Treatment of human populations with a systemic insecticide would guarantee delivery of insecticides to human feeding malaria vectors regardless of feeding location or time.
Ivermectin

- Macrocyclic lactone isolated from the bacteria *Streptomyces avermitilis*
- Mode of action – binds at subunit interfaces next to the glutamate-gated chloride (GluCl) ion channels, which distorts the channel from closed to open, hyperpolarizing the cell (Hibbs and Gouaux 2011) which leads to the paralysis of the nematode or ectoparasite musculature (Cully et al. 1994, 1996, Cane et al. 2000)
- Different class of insecticides than those used for ITNs or IRS
Modified Vectorial Capacity Equation

(Garrett-Jones 1964, Black and Moore 2005)

\[ V = \frac{ma^2pb}{-\ln p} \]

- **V** – average number of potentially infective bites that will be delivered by all vectors feeding on a single host in one day
- **p** – daily probability of adult mosquito survivorship
- **a** – daily probability an *Anopheles* feeds on a human (human bloodmeal index × feeding frequency)
- **n** – duration of the extrinsic incubation period
- **b** – vector competence (ie. proportion of *Anopheles* that ingest *Plasmodium* and successfully become infectious)
- **m** – vector density in relation to the host
Lethal concentration ivermectin for *Anopheles*:

- **dirus**: n=5029, r=6
- **sawadwongporni**: n=1431, r=4
- **campestris**: n=2786, r=4
- **minimus**: n=2376, r=6
- **gambiae**: n=2013, r=8 (reference)

Legend:
- $\text{LC}_{50}$
- $\text{LC}_{25}$
- $\text{LC}_{5}$
Simulated concentration-time profiles with respect to time above a theoretical LC$_{50}$-value

Ivermectin concentration (ng/mL) vs. Time (days)

- Blue line: Dose: 200 ug/kg
- Red line: Dose: 400 ug/kg
- Green line: Dose: 800 ug/kg

Key:
- 1.6 d
- 2.7 d
- 3.7 d

LC$_{50}$
Impact on transmission

Normal vector lifespan

Approx. 10 days after biting, vector becomes infectious
MDA alone vs. MDA + IVM

ACT given to everyone, IVM given to everyone >5yrs old, coverage=90%
Same affect as with MSAT, but more sustained reduction in transmission, especially in a low prevalence setting.
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.
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.
Corresponding MPAC question

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 programme with high population coverage in many regions. Personal repellents as programmatic interventions have shown very limited impact, but can be important for individual protection.
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 nonsupervised 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.
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.
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.
Additional MPAC questions (3)

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.
**Additional MPAC questions (4)**

What actions, if any, should be recommended for groups such as 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.

**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.
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?

See feasibility assessment....
Arjen DONDORP, Chair
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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
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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

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

Stephen VREDEN
Academic Hospital Paramaribo
Paramaribo, SURINAME

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

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

Ulie THWING
Center for Disease Control and Prevention
Jakar, SENEGAL
OBSEVERS

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Drug Resistance and Containment Unit, GMP

Marian WARSAME
Medical Officer
Drug Resistance and Containment Unit, GMP
A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

Frédéric Ariey\textsuperscript{1,2†}, Benoît Witkowski\textsuperscript{3}, Chanaki Amaratunga\textsuperscript{4}, Johann Beghain\textsuperscript{1,2†}, Anne-Claire Langlois\textsuperscript{1,2}, Nimol Khim\textsuperscript{3}, Saurin Kim\textsuperscript{3}, Valentine Duru\textsuperscript{3}, Christiane Bouchier\textsuperscript{5}, Laurence Ma\textsuperscript{5}, Pharath Lim\textsuperscript{3,4,6}, Rithea Leang\textsuperscript{6}, Socheat Duong\textsuperscript{6}, Sokunthea Sreng\textsuperscript{6}, Seila Suon\textsuperscript{6}, Char Meng Chuor\textsuperscript{6}, Denis Mey Bour\textsuperscript{7}, Sandie Ménard\textsuperscript{8†}, William O. Rogers\textsuperscript{9}, Blaise Genton\textsuperscript{10}, Thierry Fandeur\textsuperscript{1,3}, Olivo Miotto\textsuperscript{11,12,13}, Pascal Ringwald\textsuperscript{14}, Jacques Le Bras\textsuperscript{15}, Antoine Berry\textsuperscript{8†}, Jean-Christophe Barale\textsuperscript{1,2†}, Rick M. Fairhurst\textsuperscript{4*}, Françoise Benoit-Vical\textsuperscript{16,17*}, Odile Mercereau-Puijalon\textsuperscript{1,2,*} & Didier Ménard\textsuperscript{3*}
K13 SNPS are associated with clinical artemisinin resistance in Myanmar and Vietnam as well as Cambodia

Takala-Harrison, Jacob et al. submitted
Prevalence of K13 SNPs in Asia, Madagascar and Mali

% Other Mutant
- A676D
- A675V
- F673I
- D648E
- N594S
- V589I
- C580Y
- A578Y
- P574L
- R561H
- P553L
- I543T
- R539T
- G538V
- N537I
- G533A
- I526T
- E509V
- Y493H
- N490T
- C469Y
- N458Y
- G449A
- F446i
- P441L
- D281V
- E252Q
- K189T
- Wild type

Countries and Locations:
- Bin Phuc, Vietnam
- Ranong, Thailand
- Phusing, Thailand
- Mae Sot, Thailand
- Attapeu, Laos
- Pailin, Cambodia
- Rattanakiri, Cambodia
- Preah Vihear, Cambodia
- Pursat, Cambodia
- Southern China
- Shwe Kyin, Myanmar/TRAC
- Shwe Kyin, Myanmar/Plowe
- Thanyuzavat, Myanmar
- Buthidaung, Myanmar
- Antsoihy, Madagascar
- Bekily, Madagascar
- Manandriana, Madagascar
- Vatomandry, Madagascar
- Sikasso, Mali
De-novo gametocyte vs parasite clearance half-life

(24 hours to 7 days after the onset of treatment)
Frequency of K13 SNPs in 886 parasite isolates in six Cambodian provinces in 2001–2012

Ariey et al. Nature 2013
Most K13 SNPs reside in the “propeller” domains
What is antimalarial drug resistance?

- Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject” (WHO, 1973)
- Therapeutic efficacy is used as an 'alert' to drug resistance but not all treatment failures are due to resistance. Treatment failure can be due to:
  - pharmacokinetic (low absorption, increased metabolism, etc...)
  - immunity (HIV, pregnancy, etc...)
  - confirmed resistance
- Therefore other tools are needed to confirm resistance
  - pharmocokinetics
  - in vitro efficacy
  - molecular markers
Main result 1

CLINICAL INCIDENCE IS HIGHEST IN A SCENARIO WITH HIGHEST PARTNER DRUG RESISTANCE

Additional malaria cases over 5 years if resistance is at the level defined by each scenario

**Scenario 1** – Pailin
High A+P resistance

**Scenario 2** – Pursat
Low A+P resistance
More LCF than Pailin

**Scenario 3** – Tasanh
Medium A resistance

**Scenario 4** – Tasanh
High A resistance

**Scenario 5** – No A resistance
High P resistance

Additional malaria cases over 5 years (from 2015 to 2019) per 1,000 individuals

Total additional malaria cases over 5 years per 1,000 individuals due to ACT resistance:
- [0,10)
- [10,20)
- [20,35)
- [35,50)
- [50,75)
- [75,100)
- [100,125]
Main result 2

PREVALENCE IS HIGHEST IN A SCENARIO WITH BOTH ARTEMISININ AND PARTNER DRUG RESISTANCE

Absolute increase in malaria prevalence (average between 2015 and 2019)

Absolute increase in prevalence if resistance is at the level defined by each scenario

Scenario 1 – Pailin
High A+P resistance

Scenario 2 – Pursat
Low A+P resistance
More LCF than Pailin

Scenario 3 – Tasanh
Medium A resistance

Scenario 4 – Tasanh
High A resistance

Scenario 5 – No A resistance
High P resistance

H. Slater Imperial College
THE SCENARIO WITH HIGH PARTNER DRUG RESISTANCE HAS THE GREATEST IMPACT ON MORBIDITY

Total additional clinical cases and percentage increase in severe malaria cases in Africa between 2015 to 2019
Key focus areas for resistance response – many roles for Village Malaria Workers

- Surveillance and information systems
- Reaching mobile and migrant populations
  - Diagnosis, treatment, referral, BCC
- Other hard to reach populations
- Suppression of using monotherapies
- Mosquito protection indoors and outdoors
- Dealing with asymptomatic/low density parasite carriers

Sylvia Meek