Report from Drug Resistance and Containment Technical Expert Group (DRC TEG) Meeting
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Dr Allan Schapira
Member of MPAC and DRC TEG
PARTICIPANTS

- Dr Arjen DONDORP, Mahidol-Oxford Research Unit, THAILAND (Chair)
- Dr Kevin BAIRD, Eijkman Oxford Clinical Research Unit, INDONESIA
- Prof. Karen BARNES, University of Cape Town, SOUTH AFRICA
- Dr Lesong CONTEH, Institute of Global Health Innovation, Imperial College, UK
- Prof. James ELIADES, Mailman School of Public Health, Colombia U., USA
- Dr Ian HASTINGS, Liverpool School of Tropical Medicine, UK
- Dr Sylvia MEEK, Malaria Consortium, UK
- Dr Harald NOEDL, Medical University of Vienna, AUSTRIA
- Prof. Chris PLOWE, University of Maryland, USA
- Prof. Christophe ROGIER, Institut Pasteur, MADAGASCAR
- Dr Allan SCHAPIRA, PHILIPPINES
- Dr Frank SMITHUIS, MYANMAR
- Dr Julie THWING, CDC, USA
Building capacity for effective monitoring of antimalarial drug efficacy

- 14 subregional network workshops on antimalarial drug-efficacy testing were organized between 2009 and 2011, covering more than 80% of all falciparum-endemic countries.
- 7 countries: WHO training courses on TES
- Groups of clinicians and microscopists were trained as consultants to create a pool of regional experts who will provide technical support
- WHO supported over 40 malaria endemic countries on issues regarding antimalarial drug efficacy, including technical advice on protocol, data analysis, quality-assured antimalarials, PCR services.
Current status of *P. falciparum* resistance

- Artesunate + SP: Failing in many settings in Africa but still highly effective in S and W Asia, Sudan and Somalia.
- Artesunate + amodiaquine: Failing in many areas, but not in West Africa.
- Artemether + lumefantrine: Still effective everywhere, except western Cambodia.
- Artesunate + mefloquine: High failure rates in W. Cambodia, parts of Thailand.
- Dihydroartemisinin-piperaquine: High failure rates in W. Cambodia. Also, it seems, in some areas of Papua New Guinea and Rwanda.
- Artesunate–pyronaridine: Efficacy of 98%, except in Pailin (W. Cambodia), where treatment failures reached 10%.
Atovaquone-proguanil

- A-P is now used as first-line treatment under strict control in certain areas of Cambodia and Thailand.

- Mutations related to atovaquone resistance, have been reported from French Guyana, India, and in several countries in Africa. Not in South-East Asia.

- Some discussion and uncertainty about the risk of spread in case of emergence of such mutations in South-east Asia.
‘The region, where malaria parasite very clever than man’

April 2012 WHO update

%age positive Day 3, on ACT treatment

Circles: Before Nov 2010
Triangles: After
Global plan for artemisinin resistance containment (GPARC) launched January 2011

To contain or eliminate artemisinin resistance where it already exists, or to prevent it where it has not yet appeared.

- stop the spread of resistant parasites;
- increase surveillance to evaluate the presence and spread of resistance;
- improve access to diagnostics and rational treatment with ACTs
- invest in artemisinin resistance-related research.

**Tier I**: areas for which there is credible evidence of artemisinin resistance.

**Tier II**: areas are those with significant inflows of people from tier I areas, including those immediately bordering tier I.

**TEG comment**: the distinction in containment activities between tier I and tier II is subtle. There is a need to increase the perimeter for containment
Lessons from containment in Cambodia, Thailand since 2008

- The project managed to rapidly increase access to prompt diagnosis and effective treatment – village malaria workers/volunteers in Cambodia.
- Banning oral artemisinin-based monotherapies as well as enforcing the ban were successful in drastically reducing the number of offending drug sellers.
- Very high coverage rates with LLINs were achieved, but maintaining the coverage was difficult, in part due to high population mobility.
- The lowering of the burden of falciparum malaria in Pailin province (W. Cambodia) associated with increased proportion of artemisinin resistant infections.
Joint assessment of the response to artemisinin resistance in the GMS November 2011 -February 2012, funded by AusAID and BMGF

Plans and strategies are not implemented with sufficient intensity, coverage and quality. Therefore (among others):

- strengthen leadership, coordination and oversight;
- secure adequate financial resources;
- build political support;
- clarify and implement policy decisions on diagnosis and treatment;
- prioritize Myanmar while maintaining a strong response in all GMS countries.
Messaging and political commitment

- There is inadequate awareness about the magnitude, urgency and seriousness of the problem of artemisinin resistance even in governments of some affected countries.

- Under *International Health Regulations*, declaring a health threat as a global *Public Health Emergency of International Concern (PHEIC)* raises high expectations regarding full containment of the emergency; if not achieved, it will be considered failure. It took years to achieve consensus that *polio* re-emergence is a *programmatic global health emergency*, and then the polio eradication programme has still had to scale back activities in 2012 due to funding gaps.

- The TEG found it is currently inappropriate to call artemisinin resistance a PHEIC. The TEG agreed on designating resistance to artemisinin and partner drugs a growing regional emergency that represents a major threat to global malaria control and elimination efforts if not contained and eventually eliminated.
Messaging suggested by DRC TEG

- ACTs are currently failing in a geographically limited region, where resistance to both the artemisinin and ACT partner drugs is present, causing severe and worrying limitations to the available treatment options for falciparum malaria in these regions.
- This message should be balanced against the fact that over 200 million people are successfully treated globally with ACTs each year, and that access to ACT treatment has contributed importantly to the current reduction in malaria morbidity and mortality.
- Fighting antimalarial drug resistance must be a global effort starting with the implementation of the Global plan on artemisinin resistance containment (GPARC) recommendations in all endemic countries.
The TEG discussed whether messaging should convey that containment of artemisinin resistance is still feasible or that it is inevitable that artemisinin drug resistance will eventually emerge elsewhere, and that the current efforts are only buying time. There are no current data to strongly support either view. In both scenarios, containment efforts are essential, since no novel alternatives medicines to ACT will be available for at least the next few (> 5) years;

While elimination should be the end objective, it is clear that in certain settings such as Myanmar, elimination efforts will need to be preceded by a more realistic shorter term goal of malaria control aimed at preventing or delaying the spread of artemisinin resistance as well as reducing the parasite reservoir and decreasing the burden of disease;
Strengthening the messaging

- Messaging would be stronger if built on mathematical modeling. Efforts will be conducted in several areas:
  - to make the investment case;
  - to clarify possible impact of spread or emergence in Africa;
  - to show how different interventions impact on malaria disease and economic burden.
There is currently no consensus on the definition of artemisinin resistance.

WHO Working definitions:
- an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
- a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence of parasites after day 7 within 28 or 42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance).
- Identification of molecular markers are a top research priority.
Operational definitions/triggers

- If > 10% of patients are still parasitaemic at day 3, more detailed studies to confirm the presence of artemisinin resistance in the area are needed.
- However, this confirmation should not delay containment activities.
- TEG recommends that NMCPs also considers an increasing prevalence of “day 3 positivity” a possible marker of artemisinin resistance, provided that study populations are similar.
- The TEG emphasized: Threshold of 10% may not be suitable for Africa due to host immunity, even among young children. Interpretation should take into consideration trends over time, and changes in transmission intensity. The 10% threshold for “day 3 positivity” rate will be re-assessed following modeling and new evidence.
Based on reviewed data, the TEG concluded that there is currently no evidence of artemisinin resistance in *P. falciparum* outside the GMS.
Containment interventions

- For areas with limited health infrastructure: focus on scaling up basic malaria control interventions, including rapid expansion of community-based approaches. Universal coverage of vector control.
- Village malaria workers and mobile malaria workers
- Active case detection, mass or focused screening and treatment and (focused) mass drug administration are additional strategies mentioned in the GPARC for consideration. Although modeling suggests that repeated rounds of MDA could lead to elimination of the artemisinin-resistant strain, the meeting concluded that the repeated implementation, and achieving the high coverage required would be difficult to achieve in most areas.
Priorities for modeling

1. Multiple first-line treatments (MFLT)
   ● The effect of MFLT on the risk of drug resistance: while expected to decrease resistance, some argue that it could increase it, depending on genetics;
   ● whether the risk of resistance is reduced most (if at all) by different ACTs sequentially or at same time, same or different ACT in private and public sectors or different ACT in adults and children.
   ● The preliminary modeling results shall be presented at next TEG meeting and the recommendations discussed with the TEG on chemotherapy

2. Migration

3. Burden including economic losses
Testing new drugs, regimens or combinations

- TEG recommends a registry system to monitor treatment outcomes in patients treated with intravenous artesunate for severe malaria in tier I and II areas.
- A 5-day course of ACT could be evaluated in tier I areas, preferably in western Cambodia. Safety and tolerability as well as efficacy of a prolonged treatment course with an increase in total dose, to be established in clinical trials.
Entomology-related research priorities

- mapping of *Anopheles* vectors and their capacity to transmit artemisinin resistant parasites; and in particular, whether the artemisinin resistant parasites are capable of infecting other main vectors such as *A. gambiae* and *A. arabiensis*;

- operational research on implementation of personal protective measures, including protective clothing, especially in settings with outdoor biting vectors.