Drug Resistance & Containment TEG
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Update
Sylvia Meek
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State of artemisinin resistance to date

- Foci have been found in four countries in Greater Mekong subregion, mainly along international borders.
Is there evidence for emergence of artemisinin resistance in South America?

• Suriname and Guyana are showing a substantially increased proportion of day 3 positive patients after treatment with artemether-lumefantrine, TEG considered this a region of suspected artemisinin resistance

• TEG:
  – endorsed proposal to conduct detailed confirmatory studies in Suriname and Guyana
  – encouraged bordering countries, such as French Guyana, to conduct therapeutic efficacy studies (TES) strictly following the WHO protocol 2009
  – recommended strengthening the malaria control measures in these countries
Results of the TRAC study

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

• Characterization of the parasite clearance curve is considered as an important tool for measuring the therapeutic response to artemisinins.

• Tool developed by Worldwide Artemisinin Resistance Network (WWARN) requires the identification of the log-linear part of the parasite clearance curve and from this assesses the parasite clearance half-life.

• At the request of WHO, an alternative tool has been developed using an Excel®-based application, which takes into account the initial ‘lag phase’ and the terminal ‘tail phase’ of the clearance curve.

• Following the meeting Chris Plowe tested the tool using the data from the Artemisinin Resistance Confirmation Characterization and Containment (ARC3) project. Both estimators performed very similarly
Comparison of two parasite clearance estimators
**Update on molecular markers for artemisinin resistance**

- Marker not yet available
  - Although much progress has been made over the last year, and regions in the parasite genome strongly correlating with delayed parasite clearance phenotype have been identified
- It is predicted that in the near future a set of region-specific single nucleotide polymorphisms (SNPs) will be able to identify artemisinin resistant *P. falciparum* with adequate specificity and sensitivity. This would be an excellent tool to monitor the spread of artemisinin resistance in SE Asia
  - But there are probably multiple SNPs involved (e.g. a mosaic of mutations associated with the phenotype that vary among parasite populations).
- TEG recommended that additional sources of parasites (e.g. filter paper blood spots and if possible blood depleted of white blood cells) should be sampled on a more routine basis during TES and research trials and surveys, which could then be used to do the molecular analyses of resistance genes and parasite gene flow.
Update on in vitro artemisinin susceptibility testing

• Several in vitro methods for assessing artemisinin susceptibility are available for research purposes but there is no test recommended as standard method.

• Tests focusing on inhibition of ring stage development, as well as the use of short term (4-6 hours) exposure to artemisinins appear to have the best sensitivity to identify the in vivo resistant phenotype.

• Multi-pulsing and 6-day (minimum) recovery assays are showing promise.
Multiple first-line treatments: outcome of recent modeling efforts

- Implementation of multiple first-line treatments (MFLT) has been suggested as a strategy to reduce the risk of emergence and spread of artemisinin resistance.
- TEG discussed two mathematical models which yielded divergent results on the benefit of MFLT in certain settings, so that a general recommendation on the implementation of MFLT could not be given at this time.
- TEG recommended that the different modeling groups collaborate to understand the reasons for these differences. The benefits expected by MFLT should be well defined and these will vary depending on the settings.
- In future work, it will be important to address the problem of resistance to partner drugs as well, as it is also an important concern.
- A sequential deployment strategy may be difficult to implement in countries, which already have MFLT.
- Other approaches delaying resistance, such as triple combinations should also be considered.
Developments in study design and implementation of mass drug administration as a tool for eliminating artemisinin resistant malaria

- The Mahidol-Oxford Research Unit (Bangkok) is funded by Bill & Melinda Gates Foundation (BMGF) and the Wellcome Trust for a study piloting targeted malaria elimination. It is planned to target mass drug treatment to villages/areas with high *P. falciparum* prevalence rates (measured by a large-volume qPCR method with a sensitivity of around 20 parasites/ml), with the objective of eliminating falciparum malaria from those villages/areas.
- Proposed project is research not a policy recommendation. It will be important to assess not only the efficacy of the intervention, but also feasibility and acceptability.
- The main concern with this approach is how to deal with the ‘last man standing’ phenomenon, as the parasites not killed during the MDA campaign are likely to be the most resistant. One approach could be to give the 3 monthly courses of treatment with 3 different medicines.
  - TEG favored this approach and recommended modifying the protocol accordingly.
- Presence of piperaquine resistance in Western Cambodia raised the question of why this drug would be used for MDA in this area.
  - TEG stressed the need for better assessment of the strategies that work and those that are not working. Preliminary results of the study should be discussed during the next TEG meeting.
**Suggested operational research to be conducted within the context of ERAR**

- Mass drug administration (MDA) and targeted malaria elimination
- Mapping passively and actively detected cases, including asymptomatic carriers;
- New treatment modalities including new chemical entities and extending ACT treatment courses to 5 or 7 days;
- Molecular studies of resistant genes and gene flow from filter paper blood samples;
- Methods on how to control vectors and how to eliminate transmission using drug approaches in the host (primaquine and/or ivermectin).
- TEG would like to see a mechanism by which its recommendations, after review and endorsement by MPAC, are communicated to the regional steering committee (RSC), e.g. by the representation of WHO on the RSC.
What is being done in response?

• Ongoing containment activities
• Call for more action following Joint Assessment of the Response to Artemisinin Resistance
• WHO launched Emergency Response to Artemisinin Resistance (ERAR)
• New initiatives
• Political engagement (Australia 2012, Asia Pacific Leaders’ Malaria Alliance - APLMA)
Ongoing containment activities

- Myanmar MARC 2011 -
- Thailand GF R10 2011-
- Thailand/Cambodia ARCE 2008-2011
- Cambodia GF R9 2010 -
- Viet Nam 2011 -
Emergency response to artemisinin resistance (ERAR) in the Greater Mekong subregion

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

Tier I: Areas for which there is credible evidence of artemisinin resistance;

Tier II: Areas with significant inflow of people from tier I areas, including those immediately bordering tier I;

Tier III: Areas with no evidence of artemisinin resistance and limited contact with tier I areas.
Changes in Tiers
(proposed for updating following country agreement)
Update on the recent call from the Global Fund on artemisinin resistance

- Regional Artemisinin Initiative - built on the ERAR. Approximately 100 million US$ will be allocated specifically for the regional containment of artemisinin resistance with activities in Cambodia, Myanmar, Thailand, Viet Nam, and Lao PDR.

- TEG emphasised that while ultimate goal of containment efforts remains the elimination of falciparum malaria in areas with resistant parasites, some countries such as Myanmar need interim objectives to contain artemisinin resistant falciparum malaria, defined as maximum reduction of the parasite load in the population, and maximum effort to prevent or delay the spread of resistant parasites.

- Absence of spread of artemisinin resistance should be considered as an important outcome measure of containment, but difficult to assess. In addition to the goals set by the Global Fund, specific targets and indicators should be set by the countries.

- Elimination goals require strong surveillance, based on passive case detection, active case detection and identification of asymptomatic carriers using sufficiently sensitive tests.

- Evaluation of the RAI should include both performance indicators (e.g. each febrile case getting a proper diagnostic test and treatment) as well as impact measurements (falciparum incidence and prevalence) in its evaluation. Falciparum malaria incidence and prevalence are considered relevant impact measurements.
Next DRC TEG Meeting

• Main topics:
  – Elimination strategies of falciparum malaria in areas of artemisinin resistance in collaboration with WHO’s elimination team
  – approaches to address the failures of the present strategies
• Other topics:
  – updates on clinical studies of new antimalarial medicines,
  – modeling piperaquine pharmacokinetics in extended course treatments,
  – preliminary results from follow-up studies in South America on artemisinin resistance and
  – preliminary results of the pilot MDA.
• February 2014 to include a joint session with the Chemotherapy TEG
• The suggested main topics are a high priority for the group, and have not yet been extensively addressed in its deliberations