
MMV Stakeholders Meeting
Dar es Salaam, Tanzania
2 June 2011

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Global Malaria Programme

- Launched 18 November 2010
- Based on WHO antimalarial drug efficacy database
  - Contains 3932 studies representing 267 841 patients
  - For this report, 1120 studies representing 81 848 patients were included
- Data from three main sources:
  - published data, obtained by searching journal articles
  - unpublished data from reports by ministries of health, national malaria control programmes, nongovernmental organizations, research institutes and partners involved in the development of new antimalarial medicines; and
  - raw data from regular surveillance studies
Threshold levels for changing malaria treatment policy

WHO criteria 1998
- Grace
- Alert
- Action
- Change

WHO criteria 2003
- Parasitological failures
- Clinical failures
- Parasitological failures
- % failures (14 d f/up)
- % clinical failures (14 d f/up)

WHO criteria 2005
- Parasitological failures
- % failures (28 d f/up)
AQ treatment failure: Africa

![Graph showing AQ treatment failure in different regions of Africa](image.png)
AS-AQ treatment failure: Africa

- Maximum
- Median
- Minimum

Countries included:
- Madagascar
- Senegal
- Togo
- Angola
- Cameroon
- Eritrea
- Ghana
- Burkina Faso
- Uganda
- Rwanda
- Democratic Republic of the Congo
- Kenya
Correlation between AQ and AS-AQ
AL treatment failure: Africa
Parasite Clearance: Western Cambodia

(p=0.0001 for Δ slopes between sites)

Dondorp, NEJM, 2009
Percentage of positive cases on day 3 after ACT: Greater Mekong subregion
Percentage of treatment failure (up to day 28) after ACT: Greater Mekong subregion
AL treatment failure in SEA

![Graph showing treatment failure rates in SEA countries](image)
ASMQ treatment failure in Cambodia
ASMQ treatment failure in Thailand
GPARC: launched 12 January 2011

Funded by the Bill & Melinda Gates Foundation
## What has been done to date?

Many organizations and programs already involved ... but coordination lacking

<table>
<thead>
<tr>
<th>Before 2007</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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<tbody>
<tr>
<td><strong>WHO Guidelines for treatment (2006)</strong></td>
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<tr>
<td>• Danger of AR highlighted</td>
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<tr>
<td><strong>World Health Assembly</strong></td>
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<tr>
<td>• Resolution calls for ceasing provision of oral artemisinin monotherapies</td>
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<tr>
<td><strong>MALACTRES consortium created</strong></td>
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<tr>
<td>• Efforts to identify molecular marker for AR</td>
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<tr>
<td><strong>AFRO Committee</strong></td>
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<tr>
<td>• Resolution on drug resistance</td>
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<tr>
<td><strong>RBM Board Meeting</strong></td>
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<tr>
<td>• Strategy Paper on Antimalarial Resistance</td>
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<tr>
<td><strong>WWARN established</strong></td>
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<tr>
<td>• To facilitate research and info exchange on AR</td>
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<tr>
<td><strong>ARC3 project to confirm and characterize AR</strong></td>
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<td></td>
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<tr>
<td>• Coordinated by WHO-GMP; funded by BMGF</td>
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<tr>
<td><strong>ARCE project along the Thai-Cambodia border launched</strong></td>
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<tr>
<td>• Coordinated by WHO; funded by BMGF, GFATM, USAID</td>
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<tr>
<td><strong>RBM Ministerial Meeting</strong></td>
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<tr>
<td>• Call to withdraw oral artemisinin-based monotherapies</td>
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<tr>
<td>• Ministerial Commitment signed by 40 countries</td>
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<td><strong>AMFm pilot launched</strong></td>
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<tr>
<td>• Financing mechanism to expand access to quality-assured ACTs</td>
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</table>

**MMV (since 1999)**
- Primary org. conducting R&D for new antimalarials

**USP–PQM (since 2000)**
- Improve drug quality, appropriate use of drugs

**WHO**

**Global Malaria Programme**
Global Plan for Artemisinin Resistance Containment (GPARC)

**Goal:** Protect ACTs as an effective treatment for *Pf* malaria

- Define priorities to contain and prevent artemisinin resistance (AR)
- Motivate actions and provide clear accountabilities for key stakeholders
- Mobilize resources to fund AR containment and prevention
- Increase collaboration and coordination on AR containment activities
- Define governance mechanisms and indicators to assess progress

Developed with input from ~100 partners across RBM partnership
Supported by the Bill & Melinda Gates Foundation
Artemisinin Resistance: Working definition for purposes of the GPARC

"Artemisinin Resistance": working definition used to refer to

- An increase in parasite clearance time, as evidenced by > 10% of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance);

  – OR –

- Treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for 7 days, or the presence of parasites at day 3 and recrudescence within 28/42 days (confirmed resistance)
GPARC action pillars

1. Stop the spread of resistant parasites
2. Increase monitoring & surveillance to evaluate the AR threat
3. Improve access to diagnostics & rational treatment with ACTs
4. Invest in artemisinin resistance-related research
5. Motivate action and mobilize resources
GPARC recommendations customized locally (by Tier) based on degree of AR threat

Endemic country to evaluate its level of AR risk and apply recommendations to design a containment or prevention plan

Tier 1
Areas with credible evidence of artemisinin resistance

Tier II
Areas with significant inflows 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
**GPARC: summary of recommendations by Tier**

**Tier III**
- Good Control
- More routine monitoring
- Eliminate monotherapies & poor-quality drugs

**Tier II**
- Intensified & accelerated control
- Intensified monitoring, esp. on border near foci
- Actively eliminate monotherapies & poor-quality drugs
- Lower transmission; focus on mobile & migrant populations

**Tier I**
- Intensified & accelerated control to universal coverage
- Intensified monitoring, esp. around foci
- Aggressively eliminate monotherapies & poor-quality drugs
- Lower transmission; focus on mobile & migrant populations
- Consider ACD, MSAT, FSAT or MDA

*World Health Organization*
What is at stake?

Historical evidence shows resistance could threaten malaria control progress

When will we have new treatments?
Limited number of new candidates in the pipeline; most at least several years away

Current antimalarial R&D pipeline
From preclinical to Phase IV candidates

- Number of new treatment candidates
- Current pipeline compounds: 33
- Stalled compounds: 6
- Vivax: 3
- ACTs: 6
- Severe malaria: 4
- Endoperoxides: 6
- Antibiotic Combination: 3
- Remaining candidates: 5

Earliest time to launch:
- Current pipeline: 2016
- Stalled compounds: 2011
- Vivax: 2011
- ACTs: 2013
- Severe malaria: 2013
- Endoperoxides: >2016

If ACTs fail, endoperoxides most promising option
If endoperoxides ineffective against AR, antibiotic combinations most promising alternative
Beyond endoperoxides and antibiotics
- Only 5 other relevant candidates
- Most promising is NITD 609

I. Stop the spread of resistant parasites
Preventive measures to reduce transmission

Potential solutions

1. Rapidly scale-up recommended vector control measures in areas with evidence of AR or high risk of AR spread

2. Consider adding primaquine to ACT for confirmed cases at / near artemisinin resistance foci to reduce transmission (low transmission settings only)

3. To reach mobile populations, strengthen and expand access to preventive & curative services through public & private sector networks

4. Provide malaria interventions at / near the work-site, especially when workforce is largely mobile or migrant

5. Conduct operational research to determine how best to reach mobile and migrant populations with interventions
II. Increase monitoring and surveillance
Evaluate the artemisinin resistance threat – current status

Routine ACT therapeutic efficacy data unavailable in many endemic countries

Regular drug monitoring to evaluate AR threat

- Ensures countries are using the appropriate 1st line treatment
- Provides an understanding of the extent of artemisinin resistance
- Allows timely identification of new AR foci

Challenges
- Logistically difficult in some settings
- Missing tools: no in vitro test or molecular marker available
- Not feasible in areas of very low transmission
- Not always conclusive; host factors can confound results

Source: WHO database on antimalarial drug efficacy monitoring by country (referenced August 2010)
II. Increase monitoring and surveillance
Evaluate the artemisinin resistance threat

Potential solutions

1. In countries where therapeutic efficacy studies have not been performed with last 2 years, NMCPs should urgently conduct ACT efficacy monitoring

2. Revitalize subregional networks to support country monitoring efforts

3. Urgently communicate data suggestive of new AR foci

4. Where evidence of AR already exists, consider adding new sentinel sites near existing foci

5. Strengthen routine surveillance of malaria, including reporting of suspected treatment failure
III. Improve access to diagnostics and ACTs
Consistent and accurate diagnostic testing

Potential solutions

1. Accelerate universal coverage of parasitological diagnosis in public sector and formal private sector delivery channels

2. Continue to pilot new approaches to increase access to and use of parasitological diagnostics in informal private sector delivery channels

3. Continue efforts to improve RDT quality

4. Intensify efforts to educate providers and patients on importance of diagnostic testing
III. Improve access to diagnostics and ACTs

Access to affordable, quality-assured ACTs

Potential solutions

1. Ensure consistent availability of quality-assured ACTs in public sector through improved financing, procurement and distribution

2. Ensure quality-assured ACTs are available and affordable in private sector delivery channel; incorporating lessons from AMFm as they become available

3. Improve access to affordable, quality-assured ACTs in remote areas, primarily through integrated community case management

4. Improve ACT compliance by encouraging manufacture, use and financing of fixed-dose combinations and through education campaign
III. Improve access to diagnostics and ACTs
Removal of oral artemisinin-based monotherapies – current status

28 countries still allow marketing of such monotherapies...

... and 39 companies still known to produce such monotherapies

Countries providing marketing authorization¹ (as of Sept 2010)

- 16 never registered
- 34 withdrew marketing authorization
- 28 allow marketing

Oral artemisinin-based monotherapies believed to contribute to AR development and spread

1. Falciparum endemic countries which have adopted ACTs as 1st-line treatment policy
III. Improve access to diagnostics and ACTs
Removal of oral artemisinin-based monotherapies – potential solutions

Potential solutions

1. Work with governments and manufacturers to stop marketing and export of monotherapies via targeted regulatory interventions
2. Interrupt importation and wholesale of monotherapies
3. Actively engage retailers and other providers to ensure effective withdrawal
4. Educate patients on risk of monotherapies to reduce demand

Implementation requires investments and funding to strengthen National Drug Regulatory Authorities
III. Improve access to diagnostics and ACTs
Removal of substandard and counterfeit drugs

Potential solutions

1. Conduct quality control drug surveys to inform policy recommendations and to enable regulatory actions

2. Take immediate regulatory action to stop manufacture and wholesale of counterfeit drugs

3. Provide incentives and tools to help National Drug Regulatory Authorities, providers, and retailers identify and remove substandard drugs from the market

4. Educate patients on importance of using quality-assured medicines
## IV. Invest in AR-related research

<table>
<thead>
<tr>
<th>Category</th>
<th>GPARC priority</th>
</tr>
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</table>
| Laboratory research             | **Enable faster detection of resistance, e.g.**  
• Molecular basis of AR  
• Associated genotypes and phenotypes |
| Research & Development          | **Ensure availability of new treatments, e.g.**  
• New antimalarials  
• New transmission blocking formulations  
• New diagnostic tools for mass screening |
| Applied & field research        | **Determine if new or existing tools applied in novel ways can help manage AR, e.g.**  
• Epidemiological and transmission reduction tools  
• Effectiveness of multiple 1st line therapies to delay resistance |
| Operational research            | **Improve effectiveness of tools and programs in the field, e.g.**  
• Scalable models for reaching mobile and migrant populations  
• Behavioral patterns explaining consumption of monotherapy |
| Mathematical modeling           | **Predict the spread and impact of artemisinin resistance, including the impact of interventions intended to manage it** |
V. Motivate action and mobilize resources

GPARC success requires the support of many stakeholders

<table>
<thead>
<tr>
<th>Malaria-Endemic Countries</th>
<th>NGOs and implementation partners</th>
<th>Funding agencies and bi-laterals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>International &amp; local NGOs, CBOs</td>
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</tbody>
</table>

- **Malaria-Endemic Countries**
  - Malaria-Endemic Countries
  - Malaria NO MORE
  - PATH
  - Clinton Foundation

- **NGOs and implementation partners**
  - International & local NGOs, CBOs
  - Find
  - EANMAT
  - Research and academia

- **Funding agencies and bi-laterals**
  - USAID
  - DFID
  - Wellcome Trust
  - Global Programme

- **Multilaterals**
  - UNDP
  - ADB
  - World Health Organization

- **Private sector**
  - ExxonMobil
  - Sanofi Aventis
If AR spreads more quickly than anticipated, escalated response will be required.

<table>
<thead>
<tr>
<th>Situation today</th>
<th>Scenario A</th>
<th>Scenario B</th>
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<tbody>
<tr>
<td>Artemisinin resistance contained in Greater Mekong Subregion</td>
<td>Artemisinin resistance spreads beyond Greater Mekong Subregion</td>
<td>Artemisinin resistance emerges in or spreads to high transmission Tier III area</td>
</tr>
</tbody>
</table>

Potential severity of impact on malaria-related deaths

**GPARC recommendations to implement in endemic countries**

Heightened urgency: 3 actions to launch immediately
- Global advocacy to escalate AR to the top of global health and development agendas
- Intensive, coordinated containment efforts
- Significant increase in funding and potential reallocation of current funding
Cost to implement the GPARC estimated at ~$175 M USD per year

<table>
<thead>
<tr>
<th>Implementation costs</th>
<th>Annual costs (USD)</th>
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<tbody>
<tr>
<td>~$110 M USD</td>
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<tr>
<td>• Tier I costs (all recommendations)</td>
<td>~$10-20 / PAR*</td>
</tr>
<tr>
<td>• Tier II costs (Tier I costs exc. transmission reduction tools)</td>
<td>~$8-10 / PAR*</td>
</tr>
<tr>
<td>• Tier III costs</td>
<td></td>
</tr>
<tr>
<td>– Monitoring of ACT efficacy</td>
<td>~$50-100K / country</td>
</tr>
<tr>
<td>– Additional costs to enforce drug regulations</td>
<td>~$260-714K / country</td>
</tr>
<tr>
<td>• Global costs (implementation, monitoring and surveillance)</td>
<td>~$8-14M</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Research costs</th>
<th>~$65M USD</th>
</tr>
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<tbody>
<tr>
<td>• Additional non-artemisinin drug development costs</td>
<td>~$50M</td>
</tr>
<tr>
<td>• Acceleration of laboratory research</td>
<td>~$10-15M</td>
</tr>
</tbody>
</table>

Total GPARC costs

~$175 M USD

Implementation costs will vary significantly by area depending on intensity of threat and starting infrastructure
Funding for AR containment represents only a fraction of the total needed for malaria control.

Funding required for malaria control and ARC implementation and research

<table>
<thead>
<tr>
<th>Year</th>
<th>Investment (Millions)</th>
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<tbody>
<tr>
<td>2010</td>
<td>7.1</td>
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<tr>
<td>2011</td>
<td>6.6</td>
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<tr>
<td>2012</td>
<td>6.5</td>
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<tr>
<td>2013</td>
<td>6.4</td>
</tr>
<tr>
<td>2014</td>
<td>6.2</td>
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<tr>
<td>2015</td>
<td>6.0</td>
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</table>

The chart above illustrates the funding required for malaria control and ARC implementation and research from 2010 to 2015. The data shows a consistent need for funding, with slight variations each year.
## V. Motivate action and mobilize resources

### Proposed areas of involvement by constituency

<table>
<thead>
<tr>
<th>Constituency</th>
<th>Global policy &amp; norms</th>
<th>Surveillance &amp; reporting</th>
<th>Contain. &amp; implement</th>
<th>Resource mobilization</th>
<th>Advocacy &amp; political engagement</th>
<th>Research</th>
<th>Local policy &amp; regulation</th>
<th>Emergency response</th>
</tr>
</thead>
</table>
| **Endemic countries**  
Tier I, II & III | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Multilaterals**  
WHO - GMP | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Multilaterals  
WHO Regional & Country offices | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Multilaterals  
all other | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Research & academia | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **NGOs**  
International & local NGOs, CBOs | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Private sector | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Funding agencies and bi-laterals** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

1. Research conducted by WHO-TDR
Take home messages

- Artemisinin resistance is a major public health threat
  - If it were to reach Africa today, could undo a decade of progress towards achieving health-related MDGs
- Africa must be prepared
  - Routine in vivo efficacy monitoring is critical
- Africa must act now
  - Remove oral artemisinin-based monotherapies from the market
  - Ensure access to prompt diagnostic testing and treatment with ACTs of confirmed cases of falciparum malaria
- We must all support R&D for new antimalarial combinations to replace ACTs
Thank you

Keep our eye on the prize: a world free of malaria