Latest evidence on artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapies from the markets.

Asian Pacific Leaders Malaria Alliance – Access to Quality Medicines and Other Technologies Task Force Meeting
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Diagnosis, Treatment and Vaccines
Global Malaria Programme

World Health Organization
Outline

- Oral artemisinin-based medicines (oAMTs)
- Development and spread of resistance
- Research and development pipeline for antimalarial medicines
- Monitoring the implementation of WHA60.18
  - WHO web-based monitoring system (national regulatory authorities, pharmaceutical companies)
  - ACTwatch survey results: oAMTs availability
- Regulatory action
  - Country examples
  - Generic Guide
  - Challenges
- Key messages
Oral artemisinin-based monotherapies (oAMTs)

World Health Assembly Resolution WHA60.18:
"...cease progressively the provision in both the public and private sectors of oral artemisinin monotherapies..."

Caveat: The Resolution refers to phasing out oral* artemisinin-based monotherapies, i.e. tablets, capsules, suspensions.

Main factors contributing to development and spread of resistance

- Patient compliance / adherence to treatment
- Co-formulated products
- Quality of medicines (low amount of active pharmaceutical ingredients, due to e.g. poor stability or degradation)
- Migrating populations
- Weak regulatory systems
- Insufficient knowledge on prescriber and patent side
- Insufficient availability of quality artemisinin-based combination therapies (ACTs) at affordable prices

*Rectal and injectable formulations: Still required for pre-referral treatment and treatment of severe malaria
Rapid development and spread of resistance to monotherapies

<table>
<thead>
<tr>
<th>Antimalarial compound</th>
<th>Year of introduction</th>
<th>First case of resistance</th>
<th>Duration until first resistance</th>
</tr>
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<tbody>
<tr>
<td>Quinine</td>
<td>1632</td>
<td>1910</td>
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<tr>
<td>Chloroquine</td>
<td>1945</td>
<td>1957</td>
<td>12</td>
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<tr>
<td>Proguanil</td>
<td>1948</td>
<td>1949</td>
<td>1</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>1967</td>
<td>1967</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>1977</td>
<td>1982</td>
<td>5</td>
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<tr>
<td>Atovaquone</td>
<td>1996</td>
<td>1996</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Artemisinin derivatives</td>
<td>1990</td>
<td>2009</td>
<td>19</td>
</tr>
</tbody>
</table>

The spread of *Plasmodium falciparum* resistance to chloroquine
Latest evidence on artemisinin resistance
WHO Status report on artemisinin resistance (January 2014)

Confirmed foci
- Cambodia
- Laos
- Myanmar
- Thailand
- Viet Nam

Suspected foci
- Suriname
- Guyana
- French Guyana

Tier map of the Greater Mekong Subregion (January 2014)
# Medicines for Malaria Venture (MMV) Current Research and Development Portfolio

<table>
<thead>
<tr>
<th>Research</th>
<th>Translational</th>
<th>Development</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead optimisation</strong></td>
<td><strong>Preclinical</strong></td>
<td><strong>Human volunteers</strong></td>
<td><strong>Patient exploratory</strong></td>
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<td>Novartis MP</td>
<td>1 project Novartis</td>
<td>P218 DHFR</td>
<td>DSM265</td>
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<tr>
<td>GSK MP</td>
<td>3 projects GSK</td>
<td>ELQ-300</td>
<td>OZ439/FQ</td>
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<td>Sanofi MP</td>
<td>Orthologue leads Sanofi</td>
<td>21A092</td>
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<tr>
<td>AstraZeneca MP</td>
<td>Whole cell leads AstraZeneca</td>
<td>MMV390048</td>
<td></td>
</tr>
<tr>
<td>Heterocycles Celgene</td>
<td>Oxaboroles Anacor</td>
<td>SJ557730</td>
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<tr>
<td>Heterocycles Univ Campinas</td>
<td>Tetraoxanes Liverpool STC/Liverpool Univ</td>
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<td></td>
</tr>
<tr>
<td>Screening Daichi-Sankyo/GHT</td>
<td>DHODH UTSW/UW/Monash</td>
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<tr>
<td>Screening Takeda/GHT</td>
<td>Aminopyridines UCT</td>
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<tr>
<td>Screening Eisai/GHT</td>
<td>Heterocycles Dundee</td>
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<tr>
<td>Pathogen Box</td>
<td>Open Source Drug Discovery Univ Sydney</td>
<td></td>
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<tr>
<td>16 Other Projects</td>
<td>Amino-alcohols Merck Serono</td>
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</table>

MMV R&D Portfolio available via the following link: [http://www.mmv.org/research-development/rd-portfolio](http://www.mmv.org/research-development/rd-portfolio)
Oral artemisinin-based monotherapies
Web-based WHO monitoring system

http://www.who.int/malaria/monotherapy_NDRAs.pdf
http://www.who.int/malaria/monotherapy_manufacturers.pdf
ACTwatch survey results: **Private sector availability of antimalarials**
DRC 40.5% (2009) and Nigeria 35% (2011)
Regulatory action – Country examples

Benin
- Combined removal of oAMTs and chloroquine (ineffective due to P. falciparum resistance).
- Alignment of removal with large-scale deployment of ACTs.

India and Pakistan
- Coordination of initiative by the national regulatory authorities essential.
- Acceleration of procedures through support provided by the National Malaria Control Programme and WHO in both countries to accelerate the process.
- India: Need for close coordination between the federal drug regulatory authorities and the state regulatory authorities.

Cambodia and Malawi
- Comprehensive approach comprising withdrawal / suspension of marketing, manufacturing and import licenses for oAMTs.
- Cambodia: Active search and confiscation of all oAMTs, applying enforcement laws.
- Malawi: Disposal of all oAMTs in the market, followed by enforcement via quarterly inspections to all drug outlets in the private sector.
# Generic guide to phase out oAMTs from the markets

<table>
<thead>
<tr>
<th>Action</th>
<th>Task</th>
<th>Suggested approximate timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Agreement on time frame of phasing out oAMTs in synchrony with large-scale implementation of ACTs</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 2</td>
<td>Suspension of new approvals of marketing authorizations for oAMTs</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 3</td>
<td>Suspension of import licences for artemisinin or its derivatives (as API or FPP) to domestic companies exclusively marketing oAMTs</td>
<td>3–4 months</td>
</tr>
<tr>
<td>Step 4</td>
<td>Large-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapies</td>
<td>Time X</td>
</tr>
<tr>
<td>Step 5</td>
<td>Widespread availability and affordability of quality ACTs in the private sector</td>
<td>Time Z</td>
</tr>
<tr>
<td>Step 6</td>
<td>Withdrawal of marketing authorization and of manufacturing licences for oAMTs as FPPs to protect domestic markets</td>
<td>6 months after time X</td>
</tr>
<tr>
<td>Step 7</td>
<td>Suspension of export license for oAMTs as FPPs to protect export markets</td>
<td>6 months after time X</td>
</tr>
<tr>
<td>Step 8</td>
<td>Active recall of oAMTs from the market</td>
<td>3 months after time Z</td>
</tr>
<tr>
<td>Step 9</td>
<td>Enforcement activities (e.g. regular outlet inspections, confiscation and destruction of products, suspension of selling licenses, fines, prosecution)</td>
<td>Regular intervals after Step 8</td>
</tr>
<tr>
<td>Step 10</td>
<td>Monitoring to ensure complete elimination of oAMTs as FPPs from the market</td>
<td>10–12 months after time X</td>
</tr>
</tbody>
</table>
Main challenges

- **Regulatory environment** (Withdrawal of domestic licenses without suspension of export licenses in producing countries allows for oAMTs to enter poorly regulated pharmaceutical markets in endemic countries)

- **Weak enforcement mechanisms** (e.g. active recall, confiscation, destruction, regular inspections, suspension of selling licenses, ...)

- **Limited availability of quality ACTs at affordable prices in the private sector** (Limited access to ACTs often caused by slow roll-out of ACTs in the public sector and limited penetration of ACTs in the private sector)
Key messages

- Artemisinin resistance – confirmed in five countries in the Greater Mekong Subregion, suspected in three countries in South America – requires intensified action to eliminate oAMTs from the markets.

- Successful country examples show withdrawal of oAMTs from the markets is possible and requires a number of critical steps plus enforcement mechanisms.

- Government commitment and strong stewardship of national regulatory authorities is crucial to protect both domestic and export markets.
Thank you
Backup slides
## Main factors contributing to the development and spread of artemisinin resistance

<table>
<thead>
<tr>
<th>Issue</th>
<th>Potential solution</th>
</tr>
</thead>
</table>
| Patient compliance / adherence to treatment                           | • ACTs with 3-day treatment regimen  
• Patient information  
• Fixed-dose ACTs (quality, availability, price)  
• Elimination of oAMTs from the market |
| Co-formulated products                                                | • Fixed-dose ACTs (quality, availability, price)                                      |
| Quality of medicines (low amounts of active pharmaceutical ingredient, e.g. poor stability or degradation) | • Selection of pre-qualified antimalarial medicines for procurement  
• Functioning quality assurance and quality control measures at country level |
| Migrating populations                                                 | • Increase monitoring / surveillance (mass population movements from areas with high levels of resistance)  
• Improve access to rational treatment with ACTs |
| Weak regulatory system                                                | • Strengthening of national regulatory systems  
• Capacity building and structural reforms |
| Insufficient knowledge on prescriber and patient side                 | • Training and communication to change prescriber habits  
• Information campaigns for patients |
| Insufficient availability of quality ACTs at affordable prices         | Ensure large-scale availability of affordable quality ACTs and RDTs in both public and private sectors to help crowding out oAMTs and to promote rationale use of ACTs |
Epidemiological determinants of drug resistance

* From same and/or different areas through population movements

Modified from WHO Epidemiological Approach to Malaria Control. WHO Reference Code 98121
Main initiatives to implement WHO recommendations

- 2006:
  - WHO Press Release
  - Web-based monitoring system for marketing practices and position of companies and national regulatory authorities (http://malaria.who.int/)
  - Dissemination of WHO position via WHO Offices
  - WHO staff briefings, inter-country and regional meetings with MOH officials
  - WHO technical briefing on malaria guidelines and artemisinin monotherapies, Alignment of funding and procurement agencies

- 2007:
  - World Health Assembly Resolution (WHA60.18)
  - WHO informal consultation with manufacturers of artemisinin-based antimalarial

- 2010:
  - Publication of the article in the WHO Drug Information “Regulatory action needed to stop the sale of oral artemisinin-based monotherapy”
  - International Conference of Drug Regulatory Authorities (ICDRA), Singapore

- 2011:
  - World Health Assembly Resolution (WHA64.17)
  - Global plan for artemisinin resistance containment (GPARC)

- 2013:
  - Emergency response to artemisinin resistance (ERAR) in the Greater Mekong subregion, Regional Framework for action 2013-2015
Regulatory targets for phasing out oAMTs

**Outside the country**
- Manufacturing Licence
- FPP Export Licences
- Foreign FPP Manufacturers
- Marketing Authorization
- FPP Import Licences

**Inside recipient country**
- Manufacturing Licence
- API Import Licences
- Domestic FPP Manufacturers
- Domestic FPP Reconditioning
- Marketing Authorization

**Health Providers**
- Oral Artemether, Artemisinin, Artesunate, Dihydro-artemisinin, Artemotil

**Consumers**
- Artemisinin resistance