Artemisinin resistance: global situation, update and next steps

WHO Webinar

Global Malaria Programme
• Terminology: *multidrug-resistant, extensively drug-resistant and pandrug-resistance* (Magiorakos et al., 2011);

• Antimalarial drug resistance: ability of a parasite strain to survive and/or multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within tolerance of the subject;

• Multidrug resistance (MDR) requires resistance to more than two operational antimalarial compounds of different chemical classes;

• Artemisinin (partial/relative) resistance = delayed clearance does not match with the current conventional WHO 1973 definition of antimalarial drug resistance;

• ACT resistance: resistance to both compounds i.e. partial artemisinin resistance and partner drug resistance;

• ACT failure: treatment failure rate following treatment with an ACT regardless of the presence artemisinin resistance.
Why conduct Therapeutic Efficacy Studies (TES)?

- Surveillance of therapeutic efficacy (also called in vivo test) over time is an essential component of malaria control and provides
  - important information for determining whether first- and second-line drugs are still effective: and
  - the evidence-base to ministries of health to update their national malaria treatment policies;
- The WHO currently recommends monitoring the efficacy of first-line and second-line ACTs every 2-3 years in all falciparum-endemic countries. The results of TES make it possible to determine the:
  - proportion of patients who are parasitemic on day 3, which is currently the indicator of choice for routine monitoring to identify suspected artemisinin resistance in *P. falciparum*; and
  - proportion of treatment failure by 28-day or 42-day follow-up (depending on the partner drug half-life in the specific ACT); a treatment failure rate exceeding 10% should prompt a change in the national antimalarial treatment policy.
Evaluation of therapeutic efficacy study results

**Day 3:** % patients parasitemic

- < 10%
- ≥ 10% or < 10% but increasing over time

**Day 28 or 42:** % treatment failure

- < 10%
- ≥ 10%

**Interpretation**

- No evidence of resistance to artemisinin or partner drug
- Partner drug is failing
- Suspected resistance to artemisinin
- Suspected resistance to artemisinin or partner drug

**Response**

- No change in treatment policy required
- Change ACT
- Confirm resistance to artemisinin
- No change in treatment policy required
- Change ACT or discuss alternative non-ACT treatment options

Global Malaria Programme

World Health Organization
● All treatments for uncomplicated malaria are ACTs and artesunate/artemether are used for severe malaria;
● Artemisinin resistance could become total;
● Implication for the treatment of severe malaria;
● Increases the risk of de novo resistance to the partner drug and/or facilitate the selection of partner drug resistance: treatment failures are likely to increase with the resistance to partner drugs.

Consequences of artemisinin resistance

Adapted from N. White
**Timelines and key targets**

- **2006**: Early warning signs of *P. falciparum* resistance to artemisinin detected in Cambodia.
- **2008**: *P. falciparum* resistance to artemisinin first confirmed along the Cambodia-Thailand border.
- **Nov. 2008**: Artemisinin resistance containment project, supported by WHO and funded by the Gates Foundation, initiated along the Cambodia-Thailand border.
- **Jan. 2011**: WHO launches a Global Plan for Artemisinin Resistance Containment (GPARC). The GPARC sets out a high-level plan of attack to protect ACTs as an effective treatment for *P. falciparum* malaria.
The framework is based on recommendations from a joint assessment of regional response to artemisinin resistance conducted from November 2011 to February 2012 which called for a major scale-up of containment activities;

In April 2013, WHO launched the Emergency response to artemisinin resistance, in the Greater Mekong subregion; a regional framework for action 2013-2015;

Aim is not to replace existing national, regional or global strategies -- but to increase coordination, quality and coverage of interventions.
Number of ACTs failing in the GMS

High ACT failure rate (>10%) to:
- 1 ACT
- 2 ACTs
- 4 ACTs
## Rationale for malaria Elimination in the GMS

<table>
<thead>
<tr>
<th>2014</th>
<th>2015</th>
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<tbody>
<tr>
<td>Apr</td>
<td>May</td>
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<tr>
<td>28-30 April</td>
<td>Feasibility study performed on elimination in GMS</td>
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</tbody>
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### Conclusion of the feasibility study

- Artemisinin resistance has emerged independently in multiple geographic areas within the GMS, raising concerns about effectiveness of a “firewall approach”;
- Multidrug resistance including ACT resistance was reported in the GMS;
- The burden of disease in the GMS has been lowered to levels where most countries are considering, or have already committed to, elimination over the next 10–15 years;
- *P. falciparum* elimination in the GMS appears technically and operationally feasible at a reasonable cost
Subsequently, during the World Health Assembly in May 2015, WHO launched the Strategy for malaria elimination in the GMS (2015–2030), which was endorsed by all GMS countries.
## National elimination strategies in the GMS

<table>
<thead>
<tr>
<th>Country</th>
<th>Status of national malaria elimination plans</th>
<th>National malaria elimination target date</th>
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<tbody>
<tr>
<td>Cambodia</td>
<td>&quot;Malaria Elimination Action Framework (2016-2020)&quot; launched in January 2016.</td>
<td>2025</td>
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<tr>
<td>China</td>
<td>&quot;Malaria Elimination Strategy 2015-2020&quot; completed in 2015.</td>
<td>2020</td>
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<tr>
<td>Lao People’s Democratic Republic</td>
<td>&quot;National Strategic Plan for Malaria Control and Elimination (2016-2020)&quot; developed and under process of endorsement by the Ministry of Health.</td>
<td>2030</td>
</tr>
<tr>
<td>Myanmar</td>
<td>&quot;National Strategic Plan for Intensifying Malaria Control and Accelerating Progress towards Malaria Elimination 2016-2020&quot; developed and under process of endorsement by the Ministry of Health.</td>
<td>2030</td>
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<tr>
<td>Thailand</td>
<td>&quot;National Malaria Elimination Strategy 2017-2026&quot; launched in April 2016.</td>
<td>2024</td>
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<tr>
<td>Viet Nam</td>
<td>&quot;National Strategy for Malaria Prevention, Control and Elimination 2011-2020&quot; in place; detailed elimination action plan has been finalised.</td>
<td>2030</td>
</tr>
</tbody>
</table>
Timelines and key targets

2006
Early warning signs of *P. falciparum* resistance to artemisinin detected in Cambodia.

2008
*P. falciparum* resistance to artemisinin first confirmed along the Cambodia-Thailand border.°

Nov. 2008
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Jan. 2011
WHO launches a Global Plan for Artemisinin Resistance Containment (GPARC). The GPARC sets out a high-level plan of attack to protect ACTs as an effective treatment for *P. falciparum* malaria.

2013
WHO launches the *Emergency response to artemisinin resistance in the Greater Mekong Subregion, Regional framework for action 2013-15*, and establishes a regional hub in Phnom Penh, Cambodia, to coordinate multi-partner action.

Sept 2014
The WHO Malaria Policy Advisory Committee recommends the adoption of the goal of elimination of *P. falciparum* malaria in the GMS.

May 2015
GMS Ministers of Health adopt the WHO *Strategy for malaria elimination in the Greater Mekong Subregion*. The plan aims to eliminate *P. falciparum* malaria from the subregion by 2025 and all species of human malaria by 2030.

By 2020 or earlier
Transmission of *P. falciparum* malaria interrupted in all areas of multi-drug resistance, including ACT resistance.

By 2020
*P. falciparum* malaria eliminated in Cambodia.
All species of human malaria eliminated in Yunnan Province, China.

By 2025
*P. falciparum* malaria eliminated in all countries of the GMS.
All species of human malaria eliminated in Cambodia and Thailand.

By 2030
All species of human malaria eliminated in all countries in the GMS.

° Retrospective analysis has shown that artemisinin resistance likely emerged as early as 2001, before the widespread deployment of ACTs.
Thank you for your attention