Access to Quality Medicines and Other Technologies Task Force
Overview of malaria in Asia-Pacific with a focus on Artemisinin resistance

Dr Walter M Kazadi
Emergency Response to Artemisinin Resistance
Regional Hub GMS
Every year, the WHO collects, analyse, summarizes malaria surveillance data and those from special surveys in endemic countries.

WMR, the repository for available information validated by MOH.
Malaria burden - South East Asia Region, 2000 - 2012

- 1.6 billion population at risk (1 million at high risk) in 2012
- Estimated number of malaria cases: 13% decline from 31 million to 27 million between 2000 and 2012
- Reported malaria deaths: 14% reduction from 49,000 to 42,000 between 2000 and 2012
Malaria burden – Western Pacific Region, 2000 - 2012

- 711 million population at risk (70 million at high risk) in 2012
- Estimated number of malaria cases: 67% reduction from 3 million to 1 million between 2000 and 2012
- Reported malaria deaths: 49% reduction from 6900 to 3500 between 2000 and 2012
Percentage change in malaria mortality rates, 2000 - 2012

Source: WHO estimates
Percentage change in incidence of microscopically confirmed cases, 2000-2012

South-East Asia Region

Western Pacific Region
Countries projected to achieve >75% decrease in incidence of microscopically confirmed cases by 2015

South-East Asia Region

Western Pacific Region
Countries project to achieve \( \leq 75\% \) decrease in incidence of microscopically confirmed cases by 2015 or with insufficiently consistent data to assess trends.
Percentage of cases due to P. falciparum and P. vivax, 2008--2012

South-East Asia Region

Western Pacific Region
# Asia Pacific: The road to malaria elimination

<table>
<thead>
<tr>
<th>Countries in pre-elimination phase</th>
<th>Democratic People’s Republic of Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhutan</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Countries in the elimination phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sri Lanka</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country in pre-elimination phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country in elimination phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Republic of Korea</td>
</tr>
</tbody>
</table>

[World Health Organization][1]

[1]: Global Malaria Programme
Annual blood examination rate, 2008--2012

South-East Asia Region

Western Pacific Region
Estimated percentage of high risk population protected with IRS or ITNs, 2012

South-East Asia Region

Western Pacific Region
Percentage of cases potentially treated with antimalarial medicines, 2012

South-East Asia Region

Western Pacific Region
Malaria financing per person at risk, by WHO region and funding source
Pharmacokinetic properties of the artemisinin compounds
Pharmacokinetics of artesunate and dihydroartemisinin after a single intravenous dose of artesunate
Pharmacodynamic properties of artemisinin

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

48 hours

Artemisinin

Quinine
## Introduction
Since 1979, several different formulations of artemisinin have been used to treat malaria. The relation between course of treatment and recrudescence of malaria is as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment course 3 d</th>
<th>Treatment course 5 d</th>
<th>Treatment course 7 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin suppositories</td>
<td>30/56 (54%)</td>
<td>7/144 (5%)</td>
<td>1/40 (2.5%)</td>
</tr>
<tr>
<td>Artemisin tablets</td>
<td>13/25 (52%)</td>
<td>9/82 (10%)</td>
<td>2/36 (6%)</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>44/89 (49%)</td>
<td>5/97 (5%)</td>
<td>2/41 (5%)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>14/30 (47%)</td>
<td>8/97 (5%)</td>
<td>2/41 (5%)</td>
</tr>
<tr>
<td>Artemether tablets</td>
<td>12/25 (48%)</td>
<td>3/50 (6%)</td>
<td>4/205 (2%)</td>
</tr>
<tr>
<td>Dihydroartemisinin tablets</td>
<td>163/338 (48%)</td>
<td>24/373 (6%)</td>
<td>9/322 (3%)</td>
</tr>
</tbody>
</table>

*Recrudescence rates are shown as no. of recrudescences/no. treated (with percentages in parentheses).*
ACT: what kind of combination?

Total parasite biomass

Drug level

0 1 2 3 4

A

B

N. White, 1999

World Health Organization

Global Malaria Programme
Day 3 positivity rate after treatment with an artemisinin-based combination therapy, Cambodia (2001–2011)

The map shows the positivity rates in various provinces across Cambodia, with a focus on Battambang, Pailin, Pursat, Kratie, Kampong Speu, and Kampong Speu. The graphs indicate the percentage positivity rates for each year from 2001 to 2011.

- Kampong Speu: 2003

The positivity rates are represented by different drugs:
- Artemether-lumefantrine (D28)
- Artesunate-mefloquine (D42)
- Dihydroartemisinin-piperaquine (D42)
Parasite clearance time with AS+MQ in Trat province

<table>
<thead>
<tr>
<th>Province</th>
<th>Year</th>
<th>N</th>
<th>D2</th>
<th>D3</th>
<th>D7</th>
<th>PCT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trat</td>
<td>2003</td>
<td>44</td>
<td>14 (31%)</td>
<td>7 (15.9%)</td>
<td>2  (4.5%)</td>
<td>2.0</td>
</tr>
<tr>
<td>Trat</td>
<td>2004</td>
<td>15</td>
<td>2 (13.3%)</td>
<td>2 (13.3%)</td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td>Trat</td>
<td>2005</td>
<td>22</td>
<td>7 (31.8%)</td>
<td>2 (9%)</td>
<td>1  (4.5%)</td>
<td>2.3</td>
</tr>
<tr>
<td>Trat</td>
<td>2006</td>
<td>32</td>
<td>10 (31.2%)</td>
<td>7 (21.8%)</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>Trat</td>
<td>2007</td>
<td>31</td>
<td>14 (45.1%)</td>
<td>5 (16.1%)</td>
<td>0</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Courtesy Wichai Satimai & Saowanit Vijaykadga, 2008
Parasite clearance with AS+MQ in Mae Sot

Carrara, PLoS One, 2009

World Health Organization

GLOBAL MALARIA PROGRAMME
Parasite Clearance

(p=0.0001 for \( \Delta \) slopes between sites)

Dondorp, NEJM, 2009
PCT in Pailin with artesunate 6 and 8 mg/kg/d

N=40
ACT efficacy in Pailin, Cambodia (2002-2011)
D3+ and Day 28/42 outcome

- Significant contribution made by the partner drug must be taken into consideration:
  - studies conducted in GMS between 2009-2011
  - artesunate-mefloquine, artemether-lumefantrine, dihydroartemisinin-piperaquine
  - parasitemia 1000-100 000/μl

<table>
<thead>
<tr>
<th></th>
<th>TF</th>
<th>ACPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3+</td>
<td>15</td>
<td>173</td>
</tr>
<tr>
<td>D3-</td>
<td>50</td>
<td>1187</td>
</tr>
</tbody>
</table>

- OR = 2.06  p = 0.03
- PVP = 8%
- PVN = 96%
D3+ and day 28/42 outcome: role of the partner

<table>
<thead>
<tr>
<th>S</th>
<th>TF</th>
<th>ACP</th>
<th>OR</th>
<th>PVP</th>
<th>PVN</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3+</td>
<td>3</td>
<td>117</td>
<td>$1.29$, $p = 0.7$</td>
<td>3%</td>
<td>98%</td>
</tr>
<tr>
<td>D3-</td>
<td>17</td>
<td>852</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Failing partner drugs (western Cambodia and Thailand)

<table>
<thead>
<tr>
<th>R</th>
<th>TF</th>
<th>ACP</th>
<th>OR</th>
<th>PVP</th>
<th>PVN</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3+</td>
<td>12</td>
<td>56</td>
<td>$2.18$, $p = 0.04$</td>
<td>18%</td>
<td>91%</td>
</tr>
<tr>
<td>D3-</td>
<td>33</td>
<td>335</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ring-stage survival assay - RSA

Witkowski B et al., AAC, 2013
Survival rates of Cambodian parasite isolates in the RSA0–3 h, stratified by K13-propeller allele


PF3D7_1343700 polymorphisms
Suspected foci of artemisinin resistance 2013
WHO recommendations for policy change

Day 3: % patients parasitemic

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

Day 28 or 42: % treatment failures

- < 10%
- ≥ 10%

Interpretation

- No evidence of resistance to artemisinin: Partner drug is effective
- Suspected resistance to artemisinin: Partner drug is failing

Response

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

Interpretation for Day 3 parasite density:
- Include evaluation of baseline parasitemia, host immunity, and trends over time.
Definition of artemisinin resistance

- WHO is using **working definition** as below:
  - 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 after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance)
Limits of this definition

- The parasite clearance time is prone to be affected by confounding factors (known and unknown) such as splenectomy, haemoglobin abnormalities and reduced immunity.
- The proportion of patients who are parasitaemic after 3 days of treatment has been found to be a suitable though imperfect tool for screening for artemisinin resistance but is highly dependent on:
  - the initial parasitemia
  - immunity of the patients
  - the skills of the microscopists
  - D3 ≠ 72 hours
  - Artemisinin monotherapies ≠ ACTs ≠ among ACTs
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
Malaria containment/elimination zoning overview: Thailand - Cambodia

Zone 1: Elimination strategy
Zone 2: Intensified malaria control strategy
Zone 3: Routine malaria control

Note: The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations.
Source: FAO GAUL – Release January 2007; Department of Geography; Royal Government of Cambodia; Global Containment Project, WHO
Example of GPARC Implementation in Tier 1: ARCE project on Cambodia-Thailand border

- Ambitious cross-border strategy to eliminate artemisinin resistant parasites
- Coordinated by WHO working closely with Cambodian and Thailand Ministries of Health; largely funded by BMGF, GFATM, and USAID

<table>
<thead>
<tr>
<th>Target areas</th>
<th>Program combines proven malaria prevention &amp; treatment strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zone 1: areas where artemisinin tolerance detected</strong></td>
<td></td>
</tr>
<tr>
<td>- Cambodia: ~270K people in 4 provinces</td>
<td></td>
</tr>
<tr>
<td>- Thailand: ~110K people</td>
<td>Activities designed for specific cultural, social, scientific context</td>
</tr>
<tr>
<td><strong>Zone 2: areas without evidence of tolerance, but high risk (close to zone 1)</strong></td>
<td></td>
</tr>
<tr>
<td>- Cambodia: 9 provinces / ~4M people</td>
<td></td>
</tr>
<tr>
<td>- Thailand: 7 provinces / ~7M people</td>
<td></td>
</tr>
<tr>
<td>• Large-scale distribution of LLINs</td>
<td></td>
</tr>
<tr>
<td>• Free early diagnosis and treatment of malaria at the village level</td>
<td></td>
</tr>
<tr>
<td>• 24-hour health facilities to diagnose and treat malaria</td>
<td></td>
</tr>
<tr>
<td>• Intensive surveillance of positive cases</td>
<td></td>
</tr>
<tr>
<td>• Education programs</td>
<td></td>
</tr>
<tr>
<td>• Innovative approaches to reach mobile populations</td>
<td></td>
</tr>
<tr>
<td>• Efforts to stop the sale of fake and substandard drugs</td>
<td></td>
</tr>
<tr>
<td>• Stringent measures to stop the sale and use of monotherapies</td>
<td></td>
</tr>
<tr>
<td>• Pilot intensive screening in most malaria-affected border villages</td>
<td></td>
</tr>
<tr>
<td>• Basic and operational research</td>
<td></td>
</tr>
</tbody>
</table>
Cases diagnosed in Pailin province

Number of *P. falciparum* cases diagnosed by microscopy and rapid diagnostic tests in Pailin province, Cambodia (May 2008 – Dec 2012)

Containment activities started
Tiers map in GMS (Jan 2014)
Summary on malaria in Asia Pacific: burden, successes and challenges

- Good progress with some countries at the brink of elimination, but need to address the issue of heterogeneity across the Regions
- Achieving the target of 75% reduction in malaria morbidity and mortality will require additional strategic investment (Finances (both domestic and external); commodities and technologies; and BCC)
- Countries need to be supported to generate more accurate estimates to enable better monitoring and management for results
- Emergence of artemisinin resistance and its potential for spread justify a regional and global response under WHO Leadership
Summary on artemisinin resistance

What is known?

- A relatively stable genetic trait characterised phenotypically by reduced ring stage susceptibility
- Manifest by slow parasite clearance and therefore reduced parasite killing
- Can be identified ex-vivo by tests measuring ring stage susceptibility
- Associated with conserved ACT efficacy except if failing partner drug is used
- Could potentially increase risk of mortality associated with severe and complicated malaria (which is treated with artesunate monotherapy)

What is unknown?

- Molecular basis (monogenic or multigenic)
- Spread or multiple independent emergence
- Increased risk of transmission of less sensitive parasites
- Infectivity to mosquitoes outside South East Asia
- Can stable higher level resistance develop?
- Optimum treatment strategies
- How to control and eliminate it
Acknowledgements