Overview of present WHO recommendations for first and second line treatment for malaria

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Challenges with malaria treatment

- Quality of many antimalarial drugs found in endemic countries questionable
- The efficacy of (affordable) traditional antimalarial drugs has been declining due to drug resistance
- 60-90% of the population seek initial treatment from non-public sector, i.e. street vendors, kiosks where quality is uncontrolled.
- Supply of drugs is often inefficient and unreliable.
- Pharmacovigilance very weak in most affected countries
WHO recommendations for uncomplicated falciparum malaria: Artemisinin-based Combination Therapies (ACTs)

- Artemether/lumefantrine
- Artesunate + amodiaquine
- Artesunate + SP
- Artesunate + mefloquine
Why restricting to these drugs?

- Because their efficacy and safety has been demonstrated by clinical studies.
- Other combinations are under development. But
  - Chlorproguanil-dapsone has not yet been evaluated as an ACT partner drug, so there is insufficient evidence of both efficacy and safety to recommend.
  - Atovaquone-proguanil has been shown to be safe and effective as a combination partner in one large study, but its cost is very high.
  - Halofantrine has not yet been evaluated as an ACT partner medicine and there are safety concerns.
  - Dihydroartemisinin (artemimol)-piperaquine has been shown to be safe and effective in large trials in Asia, but is not included in WHO recommendations as it is not yet available as a GMP formulation, and has not yet been evaluated sufficiently in Africa and South America.
- Several other new antimalarial compounds are in development but do not yet have a sufficient clinical evidence to support recommendation here.
Why has WHO banned monotherapies

• To limit the rise of resistance to new antimalarials
• Because resistance can be prevented, or its onset slowed considerably, by combining antimalarials with different mechanisms of action
Practical aspects of treatment with recommended ACTs

• **Artemether-lumefantrine**: co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The total recommended treatment is a 6-dose regimen of artemether-lumefantrine twice a day for 3 days.

• **Artesunate + amodiaquine**: currently available as separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine, respectively. Co-formulated tablets under development. Total recommended treatment is 4 mg/kg of artesunate and 10 mg base/kg of amodiaquine given once a day for 3 days.

• **Artesunate + sulfadoxine–pyrimethamine**: currently available as separate scored tablets containing 50 mg of artesunate, and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine. Total recommended treatment is 4 mg/kg of artesunate given once a day for 3 days and a single administration of sulfadoxinepyrimethamine (25/1.25 mg base/kg) on day 1.
Practical aspects of treatment with recommended ACTs (ctd)

- **Artesunate + mefloquine**: currently available as separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively. Co-formulated tablets under development but are not available at present. Total recommended treatment is 4 mg/kg of artesunate given once a day for 3 days and 25 mg base/kg of mefloquine usually split over 2 or 3 days.

- To reduce acute vomiting and optimize absorption, the 25 mg/kg dose is usually split and given either as 15 mg/kg (usually on the second day) followed by 10 mg/kg one day later, or as 8.3 mg/kg per day for 3 days.
Recommended second-line antimalarial treatments

The following second-line treatments are recommended, in order of preference:

• alternative ACT known to be effective in the region,
• artesunate + tetracycline or doxycycline or clindamycin,
• quinine + tetracycline or doxycycline or clindamycin.
Recommendations for severe malaria

- **Quinine**: loading dose of quinine of 20 mg salt/kg. Rate-controlled i.v. infusion is the preferred route of quinine administration, but if this cannot be given safely, then i.m. injection is a satisfactory alternative.

- **Artemisinin derivatives**:
  - Artesunate IM or IV is the recommended first choice
  - Artemether IM is an acceptable alternative to quinine IV
  - Artemotil: still lack of clinical trials and pharmacokinetic data
Procurement of ACT's WHO/UNICEF Interim solution

In April 2003, tripartite meeting to discuss possible solutions and actions until a sufficient number of products are pre-qualified

WHO/UNICEF cooperation on selection and procurement.

Evaluation based on the UNICEF product quality questionnaire (similar to WHO's)
Criteria included GMP certification, registration information (countries), API, stability reports, shelf-life and storage conditions
Quality assurance based on a review of the documentation submitted jointly by UNICEF Pharmaceutical Team and WHO (EDM and Procurement with assistance from QSM when necessary)
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<tr>
<th>Continent</th>
<th>Countries</th>
<th>Drug</th>
<th>Line</th>
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<tr>
<td><strong>AFRICA</strong></td>
<td>Burundi, Cameroon, Congo, Côte d'Ivoire, Democratic Republic of Congo, Eq.</td>
<td>AS + AQ</td>
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<td>Guinea, Gabon, Ghana, Guinea, Liberia, Madagascar, Mauritania, Senegal,</td>
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<td>Sao Tomé &amp; Príncipe (ST&amp;P), Sierra Leone, Sudan (S), Zanzibar</td>
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<td>Angola, Benin, Burkina Faso, Central African Republic, Comoros, Ethiopia,</td>
<td>AL</td>
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<td>Gambia, Guinea Bissau, Kenya, Mali, Namibia, Niger, Nigeria, Rwanda,</td>
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<td>Mozambique, Djibuti, Gabon, Mozambique, Sudan (N), ST&amp;P, Zanzibar</td>
<td>AL</td>
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<td>Indonesia</td>
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<td>Afghanistan, India (5 Provinces), Iran, Tajikistan, Yemen</td>
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<td>Viet Nam</td>
<td>DP</td>
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<td>Papua New Guinea</td>
<td>AS + SP</td>
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<td>Iran, Philippines, Solomon Islands</td>
<td>AL</td>
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<td><strong>SOUTH AMERICA</strong></td>
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<td>AS + SP</td>
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<td>Bolivia, Peru, Venezuela</td>
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<td>Brazil, Guyana, Suriname</td>
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AQ=amodiaquine; AL=artemether/lumefantrine; AS=artesunate; DP=dihydroartemisinin/piperaquine; MQ=mefloquine; SP=sulfadoxine/pyrimethamine;
12–18 month lag time between ACT adoption & implementation

Cumulative No. of countries adopting ACT as 1st-line Rx

Cumulative No. of countries implementing ACT

No countries w ACT 1st line

No countries implementing ACT
Procurement of ACTs (2001–2006)

Year | Millions of treatment courses
--- | ---
2001 | 0.5
2002 | 0.6
2003 | 2.1
2004 | 5
2005 | 31.3
2006 | 65

As of 31.08.2006
2007 ACT forecast

The graph shows the forecast for the cumulative number of countries adopting ACT as first-line treatment courses, along with the actual number of countries procuring ACT and implementing it as of 2007. The forecast indicates a significant increase in the number of countries adopting ACT, with projections of 150 countries by 2007.
Expected requirements for 2007

• Note that MMSS's forecast for artemeter-lumefantrine in 2006 were ACCURATE!
• Expected requirements for A/L: between 95 and 110 million treatments
• Expected requirements for AS/AQ: between 16 and 24 million treatments
• Expected requirements for AS/SP: between 2.5 and 4 million treatments
A major bottleneck: in-country distribution

- Short shelf-life of finished products
- Limited capacity to implement at country level
- It should therefore be avoided to ship big quantities (the experience shows that 1 to 2 million treatments in one shipment is the maximum a country can handle)
A last element…..

- Evidence shows that the amount of artemisinin produced in 2006 is in excess of current/expected demand
- API price tends therefore to decrease…
- …which should translate in decreasing price for finished products!
THANK YOU!