Gaps and challenges for paediatric antimalarial medicines

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World Health Organization
Outline

- Burden of disease
- Market situation, funding
- Requirements for children medicines
- Prequalification
- Monotherapy
Why paediatric antimalarial medicines?

World Malaria Report 2008: Burden of disease

- **247 million malaria cases** (2006)
  86 % in the African region

- **881,000 malaria deaths** (2006)
  91 % in Africa
  85 % among children under 5 years

- Use of antimalarial medicine not only in confirmed malaria cases, but also for **fever cases** (up to 600 million fever cases in < 5)

Major need for antimalarial medicines for children
WHO Guidelines for the Treatment of Malaria (2006)

Artemisinin-based combination therapy (ACTs):  
- Artemether-lumefantrine  
- Artesunate + amodiaquine  
- Artesunate + mefloquine  
- Artesunate + sulfadoxine-pyrimethamine

WHO Malaria Treatment Guidelines are currently under review
ACTs: policy adoption, deployment, past procurement and 2008/09 forecast

- Millions of ACT treatment courses
- Cumulative number of countries

- ACT procured
- No countries: ACT 1st line
- No countries deploying
Increasing resources for ACTs

- Round 7 GFATM quite successful for malaria, and in Round 8 TRP approved 68% of malaria grants
- UNITAID: new funding for AIDS, TB and malaria medicines
- Affordable Medicine Facility for malaria (AMFm) – initial roll-out plan for 11 countries in April 2009, will be submitted for approval to GFATM Board on 6-8 Nov 2008
Why not adult medicines for children?

- **Sub-populations:**
  - (pre)term newborn infants
  - infants, toddlers: > 28 days - 23 months
  - children: pre-school school 2 - 5 years
  - children: post-school 6 - 11 years
  - adolescents: 12 - 16/18 years

- **Pharmacokinetics and pharmacodynamics** may be different
  (e.g. extracellular water, body fat, protein mass, liver/kidney development => absorption, distribution, metabolism, elimination)

- **Profile of adverse reactions and toxicity** may differ

- **Need for different, suitable for children pharmaceutical formulations**
Antimalarial medicine of the future

- Highly effective in curing illness – clinical and parasitological
- Very safe, including in infancy and pregnancy
- Guaranteed against resistance
- Potent anti-gametocyte (transmission blocking) activity
- Effective in all malaria species
- Have application in preventive treatment
- Fixed-dose combinations
- Simple regime – ideally single dose
- Long shelf-life (at least 3 years)
- Available in paediatric formulations and in unit-dose packaging
Additional requirements for children medicines

- Correct dosing: Need for appropriate dose-finding studies
- Ease of administration: taste, colour, flavour
- Excipients, e.g. alcohol, sugar, preservative
- Affordable price
- Formulations
  - Liquid: syrups, solutions, suspensions
  - Semi-solid: suppositories
  - Solid: tablets, (capsules, granules, pellets)
Paediatric medicines (I)

**Syrups**
- Drug solubility (dose/volume)
- API(s) compatibility with diluents
- Preferably without sugar and alcohol
- Taste (taste masking), colour, flavour
- Stability (preservatives), pH: single dose vs multidose
- Supply chain issues (large volume: transport, storage)

**Suspensions (and liquid products reconstituted from powders/granules)**
- as above
- Quality and quantity of clean water for reconstitution
- API particle sedimentation, redispersion
- Particle size/crystallinity changes on storage/shelf life

**Suppositories**
- Heat stability
- Rectal absorption
- Cultural issues
- Pre-referral treatment
### Substandard ACT: content and efficacy of preservatives in artemisinin-based dry suspensions for paediatric use

*(Atemnkeng et al. 2007)*

<table>
<thead>
<tr>
<th>Brand name/manufacturer</th>
<th>Preservative</th>
<th>Active ingredient/dose</th>
<th>Content stable*</th>
<th>Efficacy test°</th>
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<td>Sorbic acid</td>
<td>Artemether, 180 mg, dry powder 60 ml</td>
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<td>Gvither®, GVS Labs, India</td>
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<td></td>
<td>Propylparaben</td>
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<tr>
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<td>Dihydroartemisinin, 160 mg, dry powder 80 ml</td>
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<td>Not conforms</td>
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<tr>
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<td>Propylparaben</td>
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<td>Santecxin®, Shsj, China</td>
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<td>Not conforms</td>
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</table>

* preservative completely and immediately dissolved and levels unchanged during 7 days
° preservative efficacy test against *P. aeruginosa, S. aureus, E. coli, C. albicans, Z. rouxii, A. niger*
Oral solid dosage forms

- Excipients: without sugar, alcohol
- Easier to reach stability of product
- Easier to mask bitter taste of API
- Breakable or dispersible tablets easier to administer
- Breakable or dispersible tablets support clinicians to adhere to accurate dose
- Fixed-dose combinations are cost effective
- Tablets simplify supply chain management (volume: transport, storage)
<table>
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<tr>
<th>Disease</th>
<th>Name</th>
<th>Formulation and strength</th>
<th>Applicant</th>
<th>Manufacturing site</th>
<th>Packaging</th>
<th>Reference</th>
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<td>MA</td>
<td>Amodiaquine</td>
<td>Film-coated tablets 150mg</td>
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<td>MAPHAR Laboratories, Casablanca, Morocco</td>
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<td>Artecef BV</td>
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New invitation to manufacturers of antimalarial medicines - EOI for PQ (I)

1. Artemisinin-based fixed dose oral combination formulations
- Artemether + Lumefantrine: tablet 20mg+120mg; tablet 40mg+240mg; tablet 60mg+360mg; tablet 80mg+480mg
- Artesunate + Amodiaquine: tablet 25mg+67.5mg; tablet 50mg+135mg; tablet 100mg+270mg

2. Artemisinin-based fixed dose combination or co-blistered oral formulations
- Artesunate + Amodiaquine: tablet 25mg+76.5mg; tablet 50mg+153mg; tablet 100mg+306mg
- Artesunate + Mefloquine: tablet 25mg+250mg; tablet 50mg+250mg; tablet 100mg+250mg
- Artesunate + Sulfadoxine + Pyrimethamine: tablet 25mg+500mg+25mg; tablet 50mg+500mg+25mg; tablet 100mg+500mg+25mg

3. Artemisinin-based fixed dose combination or co-blistered oral paediatric formulations, preferably dispersible
- Artemether + Lumefantrine
- Artesunate + Amodiaquine
- Artesunate + Mefloquine
- Artesunate + Sulfadoxine + Pyrimethamine
New invitation to manufacturers of antimalarial medicines - EOI for PQ (II)

4. Artemisinin-based single-ingredient formulations
- Artemether: oily injection 20mg/ml; 40mg/ml; 80mg/ml
- Artesunate: powder for injection 60mg (vial)
- Artesunate: suppositories 50mg; 100mg; 200mg; 400mg
- Artesunate: tablet* 25mg; 50mg; 100mg

5. Other antimalarial medicines
- Amodiaquine: tablet 153mg (or 200mg as hydrochloride)
- Mefloquine: tablet 250mg
- Sulfadoxine + Pyrimethamine: tablet 500mg+25mg

* Artesunate tablets to be used only in combination with either Amodiaquine, Mefloquine or Sulphadoxine + Pyrimethamine
Manufacturers of artemisinin monotherapies: 41/121 expressed intention to comply with WHO
Thank you