ESSENTIAL MEDICINES FOR CHILDREN

Suzanne Hill

October 2006
What is the problem?

- Children are therapeutic orphans
  - Lack of appropriate clinical trials
  - Lack of licensed medicines
  - Lack of formulations
  - Lack of information

- Initiatives so far concentrated on:
  - Developed country regulatory structures (eg FDA, EMEA)
  - Developed country drug information (eg BNF-C)
  - HIV (eg new public private partnership)
For example…

- Creation of a Paediatric Committee at EMEA

- Requirements and Rewards/Incentives for medicinal products still under patent, orphan drugs and for off-patent medicinal products Paediatric Investigation Plans (PIP)

- Other measures
Patent-protected products

- Obligation to submit results of studies conducted according to agreed Paediatric Investigation Plan (PIP) at time of marketing authorisation, or variation (exclude generics)

  If not: Invalid application for MA

- 6-month extension of the patent protection (= Supplementary Protection Certificate)

- For orphan drugs, + 2 yrs market exclusivity
Obvious gaps

- Essential medicines list – paediatrics
- Formulations eg fixed dose combinations for malaria, TB, HIV
- Medicines for other chronic and acute diseases (eg epilepsy)
- Prescribing information, standard treatment guidelines
- International regulatory standards, including quality
- Market incentives for appropriate drug development
- International safety monitoring and post-marketing surveillance
Plan

Work on a global project to make paediatric medicines a priority:

- Add missing essential formulations to the Model list in 2007; advise on doses
- Develop EML for children (2007-8)
- Update treatment guidelines (2007-9)
- Develop paediatric prescribing information – a formulary
- Develop effective methods for provision of information at the point of care
- Collaborate with regulatory authorities to encourage appropriate drug development and approval processes in all regulatory authorities
- Develop quality standards for paediatric medicines
- Advocate for the development of paediatric medicines by the industry
- Develop a system for enhancing safety monitoring of medicines in children
- Provide guidance on procurement and supply of paediatric medicines
What has been done so far…essential medicines

- Review of current EML identifying paediatric gaps
  - Applications for isoniazid 50mg, pyrazinamide 150mg, phenobarbitone injection, caffeine citrate, several others
    http://mednet3.who.int/EML/expcom/expcom15/applications/

- Meeting to review ARVs needed for children

- Post marketing surveillance proposal

- Preliminary survey of countries about paediatric medicines, prices, guidelines, information

- Review of regulatory requirements as preliminary for discussion

- Commence review of standard treatment guidelines ('Blue Book')
Essential medicines

- **The concept of essential medicines**
  A limited range of carefully selected essential medicines leads to better health care, better drug management, and lower costs

- **Definition of essential medicines**
  Essential medicines are those that satisfy the priority health care needs of the population

  (Report to WHO Executive Board, January 2002)
The Essential Medicines Target

All the drugs in the world

Registered medicines

National list of essential medicines

Levels of use

Supplementary specialist medicines

Private sector

Hospital

Referral hospital

Health center

CHW dispensary

S

S
**EVIDENCE:** trials comparing monotherapies with ACTs

**Interventions:** single drug (oral AQ, MQ or SP) compared with single drug in combination with AS (both oral)

**Summary of RCTs:** one meta-analysis of 11 RCTs has been conducted. This found a clear benefit of adding 3 days of AS to AQ, MQ or SP for uncomplicated malaria. The combination treatment resulted in fewer parasitological failures at day 28 and reduced gametocyte carriage compared to the baseline value. Adding AS treatment for 1 day (6 RCTs) was also associated with fewer treatment failures by day 28 but was significantly less effective than the 3-day regimen (OR: 0.34; 95% CI: 0.24–0.47; p < 0.0001).

**Expert comment:** the addition of AS to standard monotherapy significantly reduces treatment failure, recrudescence and gametocyte carriage.

**Basis of decision:** systematic review.

**Recommendation:** replace monotherapy with oral ACTs given for 3 days.

---

*See also Annex 7.1.*
EVIDENCE: trials comparing ACTs

Interventions: *oral AL, AS+AQ, AS+MQ, AS+SP*

Summary of RCTs: AL 6-dose regimen compared with 4-dose regimen; 6 doses resulted in higher cure rate in 1 trial in Thailand (RR: 0.19, 95% CI: 0.06-0.62). AS+MQ compared with AL 6-dose regimen; systematic review including 2 small RCTs from Thailand. Higher proportion of patients with parasitaemia at day 28 with AL but difference not statistically significant. One additional RCT in Lao People's Democratic Republic also reported higher proportions of patients with parasitaemia at day 42 with AL but also not statistically significant. AS+AQ compared with AL 6-dose regimen: 1 trial in Tanzania found a significantly higher proportion of parasitological failures on day 28 with AS+AQ.

No trials of AL compared with AS+SP.

Expert comment: the efficacy of ACTs with AQ or SP as partner medicines is insufficient where cure rates with these medicines as monotherapies is less than 80%. The efficacy of AL and AS+MQ generally exceeds 90% except at the Thai-Cambodian border, where AL failure rate was 15%.

Basis of decision: expert opinion.

Recommendations

1. Use the following ACTs: AL (6-dose regimen), AS+AQ, AS+MQ, AS+SP.
2. In areas with AQ and SP resistance exceeding 20% (PCR-corrected at day 28 of follow-up), use AS+MQ or AL.
### 6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>amodiaquine</td>
<td>tablet, 153 mg or 200 mg (base)</td>
</tr>
<tr>
<td></td>
<td>* amodiaquine should preferably be used as part of combination therapy</td>
</tr>
<tr>
<td>artemether + lumefantrine</td>
<td>tablet, 20 mg + 120 mg</td>
</tr>
<tr>
<td></td>
<td>* recommended for use in areas with significant drug resistance and not</td>
</tr>
<tr>
<td></td>
<td>in pregnancy or in children below 10 kg</td>
</tr>
<tr>
<td>chloroquine</td>
<td>tablet 100 mg, 150 mg (as phosphate or sulfate); syrup, 50 mg (as phosphate or sulfate)/5 ml; injection 40 mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule</td>
</tr>
<tr>
<td>primaquine</td>
<td>tablet, 7.5 mg, 15 mg (as diphosphate)</td>
</tr>
<tr>
<td>quinine</td>
<td>tablet, 300 mg (as bisulfate or sulfate); injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule</td>
</tr>
</tbody>
</table>

#### Complementary List

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>artemether</td>
<td>injection, 80 mg/ml in 1-ml ampoule</td>
</tr>
<tr>
<td>artesunate</td>
<td>tablet, 50 mg</td>
</tr>
<tr>
<td>doxycycline</td>
<td>capsule or tablet, 100 mg (hydrochloride)</td>
</tr>
<tr>
<td></td>
<td>(for use only in combination with quinine)</td>
</tr>
<tr>
<td>mefloquine</td>
<td>tablet, 250 mg (as hydrochloride)</td>
</tr>
<tr>
<td>sulfadoxine +</td>
<td></td>
</tr>
<tr>
<td>pyrimethamine</td>
<td>tablet, 500 mg = 25 mg</td>
</tr>
</tbody>
</table>
**15th Expert Committee on the Selection and Use of Essential Medicines**

**Intended applications:**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Formulation</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>emtricitabine and tenofovir disoproxil fumarate fixed-dose combination</td>
<td>Tablet 200 mg emtricitabine and 200 mg tenofovir DF, equivalent to 245 mg of tenofovir disoproxil</td>
<td>Daniel P. Kates, M.D., Medtronic, Medical Communications, Medtronic Inc.</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td></td>
<td>David Watters and Malak, Chapel, (ISP)</td>
</tr>
<tr>
<td>morphine</td>
<td>Free release tablet</td>
<td>P.H. vanex, supported by the International Association for Hospital and Palliative Care</td>
</tr>
<tr>
<td>tenofovir disoproxil fumarate TDF</td>
<td>Tablet 300 mg tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil</td>
<td>Daniel P. Kates, M.D., Medtronic, Medical Communications, Medtronic Inc.</td>
</tr>
</tbody>
</table>

**Intended applications for paediatric medicines:**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Formulation</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenobarbitone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- application for duration</td>
<td>Injectable 0.1mg/mL, Ltd</td>
<td>Supported by Department of Child and Adolescent Health, WHO; prepared by Dr. J. Weinreb, South Africa</td>
</tr>
<tr>
<td>- evidence table</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EML 2005</td>
<td>Core</td>
<td>Complementary</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>Total No of medication listings</td>
<td>284</td>
<td>84</td>
</tr>
<tr>
<td>Listings not assessed</td>
<td>129</td>
<td>45</td>
</tr>
<tr>
<td>Listings assessed</td>
<td>155</td>
<td>39</td>
</tr>
<tr>
<td>PF indicated</td>
<td>119</td>
<td>28</td>
</tr>
<tr>
<td>PF not indicated</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>PF indicated and on the list</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>PF indicated and not on the list</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td>PF indicated, not on the list, duplicate listings removed</td>
<td>59</td>
<td>23</td>
</tr>
<tr>
<td>PF indicated, not on list and available*</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>PF indicated, not on list and not available*</td>
<td>30</td>
<td>21</td>
</tr>
</tbody>
</table>
Plan

Work on a global project to make paediatric medicines a priority:

- Add missing essential formulations to the Model list in 2007; advise on doses
- Develop EML for children (2007-8)
- Update treatment guidelines (2007-9)
- Develop paediatric prescribing information – a formulary
- Develop effective methods for provision of information at the point of care
- Collaborate with regulatory authorities to encourage appropriate drug development and approval processes in all regulatory authorities
- Develop quality standards for paediatric medicines
- Advocate for the development of paediatric medicines by the industry
- Develop a system for enhancing safety monitoring of medicines in children
- Provide guidance on procurement and supply of paediatric medicines
Thank you

www.who.int/medicines