Availability of Essential Medicines for Children in South Africa

Situation analysis and what regulators could do to improve it

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Essential Drugs Programme: South Africa
STGs and EDL for hospital level: Paediatrics

• 2\textsuperscript{nd} edition was published in \textbf{2006}
• Conditions: 277; medicines listed: 314
  ○ ± 66\% registered for use in children
  ○ \textbf{24\% off label}
  ○ 4 \% extemporaneous preparation
    incl. isoniazid syrup, caffeine, zinc
  ○ 1 \% not available
    incl. phenobarbitone, chloromycetin eye ointment, esmolol
• 3\textsuperscript{rd} edition – review currently under way
# Grading of evidence simplified

<table>
<thead>
<tr>
<th>Level</th>
<th>Good quality evidence</th>
<th>Limited quality patient orientated evidence</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>~ Systematic review of RCT with consistent findings</td>
<td>~ Systematic review of lower quality studies or studies with inconsistent findings</td>
<td>Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease oriented evidence (intermediate or physiological outcomes only), or case series</td>
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<tr>
<td></td>
<td>~ High quality individual RCT</td>
<td>~ Lower quality clinical trial</td>
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<td>~ Cohort studies</td>
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<td>~ Case control studies</td>
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Challenges regarding evidence based decision making for paediatrics

- Availability of good quality evidence
  - case control or case reports
- Medicines – standard of care
  - Insufficient pharmacovigilance studies
  - Paucity of randomised studies
  - Review indicators: new issues of safety or efficacy
- Capacity to critically evaluate the data available
Guideline for reviewers

• Systematic, unbiased, and transparent approach to interpreting existing, often incomplete evidence by different types of experts

• Identify robust and unbiased assessments that are available internationally and “globalise the evidence, localise the decision”.

• Not include any medicine not registered/available unless there is no alternative

Medicine technical report

Peer review, consensus based on available
Epidemiology in relation to EML
Leading causes of Natural Death: Children 0-14 years

Basis for the selection of conditions

• **31**% population under 15 years
• 1997 – 2007, 50% of deaths in children < 15 years reported due to:
  – Perinatal deaths: Respiratory, cardiovascular and digestive disorders in the perinatal period (P20-P29; P75-P78, P90-P96) – [186 443]
  – Intestinal infectious diseases (A00-A09) – [51 797]
  – Influenza and pneumonia (J10-J18) – [34 680]
  – Malnutrition (E40-E46) – [16 090]
  – Tuberculosis (A15 - A19) – [10 949]
Perinatal deaths
STGs and medicines

• 2006 edition, prematurity and neonatal conditions consolidated into a new chapter
  – Heart failure in neonates

• Neonatal apnoea
  – No registered formulation of caffeine available since 1998

• Neonatal seizures
  – Phenobarbitone discontinued by manufacturer in 2005
    – Currently obtained using compassionate use flexibility

• Heart failure in neonates
  – Off-label use of captopril, morphine and spironolactone
Tuberculosis (A15 - A19)
Tuberculosis (A15 - A19)

• Prophylaxis
  – **Isoniazid** paediatric formulation not available, crush tablets or extemporaneous preparation

• Primary TB
  – Lack of good quality data on duration of therapy for different types of TB and TB associated with HIV disease
  – Currently, quality problems with paediatric FDC formulations; not available.
  – Compassionate use (Section 21 approval)

• MDR TB
  – No registered oral paediatric formulations for MDR TB
ARVs registered for use in children

1998
• Lamivudine and zidovudine (included in STGs for PEP)
• 6 registered paediatric formulations

2006
• ARV included in STGs
• Regimens combination of 3 medicines. 7 ARVs included in guidelines
• But ...no registered paediatric formulation for efavirenz
• 13 additional ARVs registered including 7 generics
  [zidovudine (2), nevirapine (2), lamivudine (3)]

2010
• 23 additional ARVs of which 21 generics
  [zidovudine (6), nevirapine (3), lamivudine (5),
    didanosine (2), abacavir (5)]
ARVs registered for use in children

- Total: 43
  - Generics: 29
  - Originator: 14

- 2010:
  - Generics: 22
  - Originator: 2

- 2006:
  - Generics: 13
  - Originator: 7

- 1998:
  - Generics: 6
  - Originator: 6
Summary

• Off-label use
  – nurse prescribers at PHC lacks embedded knowledge to ensure safe use
  – ethical issues of using data extrapolated from adults
  – anecdotal evidence based on use, standard of care
  – adult formulations – dosing errors

• Extemporaneous preparation
  – Stability of formulations
  – Quality assurance of excipients
  – Impact on service delivery

• Compassionate use (Section 21)
  – No accountability by applicant
  – No obligation to provide data
  – Risk of compromising quality of care due to poor supply
What regulators can do to improve
Facilitate research in children by:
• Developing paediatric specific clinical trial guidance documents, with careful attention to issues such as:
  * PK studies in children
  * Standard of care
  * Dose selection
  * Bridging trials
  * Protection of vulnerable groups
• Collaborate in developing ethical frameworks for the approval of clinical trials involving vulnerable populations such as children.
• Create a regulatory condition for marketing approval that would require test data from children.
• Develop more defined policies wrt off label use in children.
• Provide guidance on the determination of doses in children for marketing approval.
• Mandatory pharmacovigilance for medicines approved for children where data is not strong.
• Conditional registration whereby registration status is only confirmed once phase IV data in children has been submitted.
• Create a framework for co-operation among regulators
• Extemporaneous preparations
  – Guidelines regarding stability
  – Safety of excipients used
Thank you
Side bar (in case of questions about process)
Step 1
Request comment from wider stakeholders
Call up notice

Step 2
Expert Committee
Review comments, guidelines and medicines

Step 3
NEDL Committee

Step 4
Request comment from wider stakeholders

Step 5
Expert Committee
Review comments
Editing and formatting

NEDL Committee
Ratification of final text

Typesetting and printing

Distribution
and implementation
What have we done

- Constitution of the Expert Review Committee
- Governance issues
- Stakeholder consultation
- Procedure for review plus guidelines for reviewers
- Motivation to put a new medicine on EML with guidelines
- Cost analysis – affordability, cost minimisations
Basis for review

- Previous STG and EML
- Technical summary of the last review
- Latest edition of the STG and EML for PHC
- Various Guidelines
- Submissions tabled during the call up notice
- A literature survey
- Health technology assessment

**Medicine technical report**

Peer review, consensus based on available evidence