

WHO Guideline Review (Essential Medicines List for Children) Report

Introduction

The inequity of access to medications for children has been recognized for many years. The scarcity of age-appropriate formulations, including life-saving antiretroviral and artemisin in combination therapies for malaria, has highlighted many other problems related to medicines for children. These include inadequate prescribing and dosing information as well as the absence of basic evidence about efficacy and safety. Children, and particularly newborns, suffer from different diseases than do adults and may require different medicines. Children differ in the way they absorb, metabolize and excrete drugs, and behavioural and developmental issues complicate their treatment. Age-related differences also mean that many medications have different therapeutic effects and adverse reactions in children compared to those in adults.

Guideline	Web address
Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access	http://www.who.int/hiv/pub/guidelines/art/en/index.html
Guidance for national tuberculosis programmes on the management of tuberculosis in children	http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_2006.7.htm
Guidelines for the treatment of malaria	http://www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=662
Managing newborn problems: a guide for doctors, nurses, and midwives	http://www.who.int/reproductive-health/publications/mnp/index.html
Pocket Book of Hospital Care for Children Management of common illness with limited resources	http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm
Pregnancy, childbirth, postpartum and newborn care: A guide for essential practice	http://www.who.int/reproductive-health/publications/pcpnc/
Preventive chemotherapy in human helminthiasis : coordinated use of anthelmintic drugs in control interventions : a manual for health professionals and programme managers	http://www.who.int/bookorders/anglais/catalog_suj1.jsp?sesslan=1&hidsubject=60305

As part of the project to identify essential medicines for children and thus potentially improve access to them, a comprehensive review of the existing clinical guidelines for childhood illnesses was carried out. The objectives of the review were:

- (i) Identify all medicines, by active component, dosage form, strength and indication that are currently recommended for use in children in WHO treatment guidelines

- (ii) To identify any discrepancies between the medicines recommended in a treatment guideline and those currently listed on the WHO Model List of Essential medicines
- (iii) To develop a priority list of medicines for evidence-based reviews, to facilitate a decision on whether they are essential medicines for children
- (iv) To provide feedback to the authors of the treatment guidelines for possible modification of treatment recommendations

Methods

Seven WHO guidelines were evaluated as part of this review. Guidelines included the most recent and comprehensive WHO guidelines for priority diseases and those recommended by the Department of Child and Adolescent Health and Development (CAH).

The guidelines reviewed are listed in the table below, with the relevant web addresses for each:

Reviewed guidelines and corresponding web addresses

An electronic version of each guideline was searched to locate all mentions of a medicine indicated for use in children. All medicines found were marked in the PDF file for easier follow up and review. Each independent record for a medicine was defined as a chemical component and dosage form/strength. For example, artesunate 50 mg suppository was listed separately from artesunate 100 mg suppository.

A Microsoft Excel table was created for each guideline that had the following information:

- Item (generic name of medicine)
- Form (tablet, capsules, solution for injection)
- Dosage
- Indication
- Age and Dosage (dosages corresponding to age and weight)
- Listed in Core EML (Yes/No)
- Section in Core EML
- Listed in Complementary EML (Yes/No)
- Location (Page and chapter in guideline)

In total, seven separate tables were created and all listed products were compared with the Essential Medicines Core and Complementary lists. All data extraction was double checked.

After generating a list of medicines for each guideline, a summary list of all original products was created. This included every product that was not mentioned in the WHO EML (either Core or Complementary lists). A column was created in the table to record information that might explain discrepancies between the guidelines and the Model List. Individual records were compared with the 14th EML, lists of Essential Medicines from 1977-2005 and with new medicine applications for the 15th EML. The final summary table shows the number of

individual products found in each guideline, the numbers mentioned in EML Core and Complementary lists, and the number of products not mentioned in the 14th EML.

Results

The numbers of original products found in each of the seven guidelines as well as the numbers of products listed in the 14th EML Core and Complementary lists and numbers not listed are shown in the following table.

Table 1. Summary of individual products in each guideline

	Original products	Number of products listed in Core EML	Number of products listed in Complementary EML	Number of products NOT listed in EML
1. Pocket Book of Hospital Care for Children Management of common illness with limited resources	203	123	7	73
2. Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice	12	7	1	4
3. Guidelines for the treatment of malaria	15	7	3	5
4. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access	36	32	0	4
5. Guidance for national tuberculosis programmes on the management of tuberculosis in children	23	9	8	6
6. Managing newborn problems: a guide for doctors, nurses, and midwives	32	21	1	10
7. Preventive chemotherapy in human helminthiasis : coordinated use of anthelmintic drugs in control interventions	7	6	1	0

Summarizing the data, there are 88 original products that are recommended in WHO guidelines for the treatment of neonates and children but are not listed in the 14th WHO EML. This information will be a useful basis for harmonizing the medicines mentioned in guidelines with those on the Essential Medicines List. Tables 2-6 in the Annex list the medicines and the issues identified.

Annex

Table 2: Medicines deleted from EML

Item	Form	Reason	Reference	Location
Aminophylline	250 mg/10 ml vial, solution for injection, IV	Added to Complementary list 2003. Deleted 2005.	1	3.1.3 Page 55; 62
Aminophylline	tablets: 100 mg	Added to Complementary list 2003. Deleted 2005.	1	Appendix 2 Page 327
Aminophylline	tablets: 200 mg	Added to Complementary list 2003. Deleted 2005.	1	Appendix 2 Page 327
Ipecacuanha, paediatric	not mentioned	Deleted 2003	1	1.5.1 Page 26
Nalidixic acid	250 mg tablet	Deleted 2005	1	Appendix 2 Page 341
Pethidine	oral, form not mentioned	Deleted 2003 from Complementary List	1	8.7.1 Page 222
Pethidine	solution for injection	Deleted 2003 from Complementary List	1	10.4 Page 275
Silver nitrate	1% eye drops	Deleted 2005	2	Page D19

Table 3: Medicines with applications for the 15th EML

Item	Form	Reason	Reference	Location
Artesunate	60 mg artesunic acid for injection (dissolved in 0.6 ml of saline/sodium bicarbonate and then in 3.4 ml of saline/glucose solution)	discrepancy in form; mentioned in Complementary list	1	Appendix 2 Page 329
Artesunate	suppository 100-mg	discrepancy in form; mentioned in Complementary list	3	page 51
Artesunate	suppository 400-mg	discrepancy in form mentioned in Complementary list	3	page 51
Caffeine citrate	oral, form not mentioned		1	3.1.3 Page 55
Caffeine citrate	solution for injection, IV		1	3.1.3 Page 55
Cefalexin	250 mg tablet		1	Appendix 2 Page 331

Item	Form	Reason	Reference	Location
Phenobarbital	vial 200 mg/ml diluted with 4 ml sterile water	discrepancy in form	1	Page 66
Vitamin A	100 000 IU capsule	discrepancy in form	1	Appendix 2 Page 346
Vitamin A	50 000 IU capsule	discrepancy in form	1	Appendix 2 Page 346

Table 4: Medicines with discrepancies in dosage form

Item	Form	Reason	Reference	Location
Ampicillin	vial of 250 mg mixed with 1.3 ml sterile water to give 250 mg/1.5 ml, solution for injection, IM, IV	discrepancy in form	1	3.7 Page 49; 3.8 Page 50
Ampicillin	250 mg tablet	discrepancy in form	1	Appendix 2 Page 328
Artemether	40 mg/1 ml ampoule, solution for injection, IM	in EML as a combination artemether + lumefantrine	1	Appendix 2 Page 329
Artesunate	suppository, 50-mg	discrepancy in form mentioned Complementary list	3	page 51
Benzathine benzyl penicillin	solution for injection, IM: vial of 1.2 million units mixed with 4 ml sterile water	discrepancy in form	1	3.13.1 Page 61
Ceftriaxone	vial of 2 g mixed with 19 ml of sterile water to give 2g/20 ml	discrepancy in form mentioned in Complementary list	1	Appendix 2 Page 331
Chloramphenicol	eye drops	discrepancy in form	1	7.4 Page 176
Chloramphenicol	eye ointment	discrepancy in form	1	3.12.2 Page 59
Chloramphenicol	125 mg/5ml suspension (palmitate), oral	discrepancy in form	1	Appendix 2 Page 332
Ciprofloxacin	ear drops	discrepancy in form	1	6.7.3 Page 163
Ciprofloxacin	100 mg tablet	discrepancy in form	1	Appendix 2 Page 333

Item	Form	Reason	Reference	Location
Cloxacillin	250mg vial mixed with 1.3 ml sterile water to give 250 mg/1.5 ml	discrepancy in form	1	Page 64
Cloxacillin	250 mg capsule	discrepancy in form	1	Appendix 2 Page 334
Codeine	15 mg tablet	discrepancy in form	1	Appendix 2 Page 334
Dexamethasone	0.5 mg tablet	discrepancy in form	1	Appendix 2 Page 335
Dexamethasone	5 mg/ml, solution for injection	discrepancy in form	1	Appendix 2 Page 335
Didanosine	oral solution from paediatric powder/water: 10 mg/ml (in many countries must be made up with additional antacid)	discrepancy in form	4	Page 110, 111, 112
Didanosine (ddI, dideoxyinosine)	enteric coated powder in capsules 30 mg (=25 mg)	discrepancy in form	1	8.2.1 Page 208, Table 23 and Page 350
Didanosine (ddI, dideoxyinosine)	enteric coated powder in capsules 60 mg (=50 mg)	discrepancy in form	1	8.2.1 Page 208, Table 23 and Page 350
Didanosine (ddI, dideoxyinosine)	enteric coated powder in capsules 115 mg (=100 mg)	discrepancy in form	1	8.2.1 Page 208, Table 23 and Page 350
Didanosine (ddI, dideoxyinosine)	enteric coated powder in capsules 170 mg (=150 mg)	discrepancy in form	1	8.2.1 Page 208, Table 23 and Page 350
Furosemide	20 mg tablet	discrepancy in form	1	Appendix 2 Page 338
Gentian violet	1% solution	discrepancy in form	1	8.4.4 Page 218
Gentian violet	0.25% solution	discrepancy in form	1	8.7.4 Page 223
Iron	Iron/folate tablet (ferrous sulfate 200 mg + 250 µg folate = 60 mg elemental iron)	discrepancy in form	1	Appendix 2 Page 339
Iron	Iron syrup (ferrous umarate, 100 mg per 5 ml = 20 mg/ml elemental iron)	discrepancy in form	1	Appendix 2 Page 339
Kanamycin	250 mg vial (2 ml at 125 mg/ml), solution for injection, IM, IV	discrepancy in form mentioned in Complementary list	1	Appendix 2 Page 339

Item	Form	Reason	Reference	Location
Kanamycin	75 mg per 2 ml vial = 37.5 mg/ml, solution for injection, IM	discrepancy in form mentioned in Complementary list	2	Page K12
Lignocaine	1% lignocaine, solution for injection	discrepancy in form	1	1.7 Page 35
Lignocaine	0.5% solution for injection	discrepancy in form	6	P-43
Lopinavir / ritonavir	tablets: 200 mg lopinavir + 50 mg ritonavir	discrepancy in form	4	Page 122, 123, 124
Nelfinavir	tablet: 625 mg	discrepancy in form	4	Page 120, 121
Nystatin	(100 000 units/ml) suspension, oral	discrepancy in form	1	8.4.4 Page 218
Nystatin	cream	discrepancy in form	6	F-131
Ofloxacin	ear drops	discrepancy in form mentioned in Complementary list	1	6.7.3 Page 163
Polyvidone iodine	2.5% eye drops	discrepancy in form	2	Page D19
Quinine	IV (undiluted): quinine dihydrochloride injection 150 mg/ml (in 2 ml ampoules);	discrepancy in form	1	Appendix 2, Page 344
Quinine	oral: quinine sulfate 200 mg tablet	discrepancy in form	1	Appendix 2, Page 344
Saquinavir	soft gel	discrepancy in form	1	8.2.1 Page 208, Table 23 and Page 351
Saquinavir	tablets: 500 mg	discrepancy in form	4	Page 119
Tetracycline	eye drops	discrepancy in form	1	7.4 Page 176
Tetracycline	250 mg tablet	discrepancy in form	1	Appendix 2 Page 346
Vitamin K (phytomenadione)	1 ampoule (1 mg/0.5ml or 1 mg/ml), solution for injection, IM	discrepancy in form	1	3.3 Page 46
Zinc	tablet (20 mg)	discrepancy in form	1	5.2.2 Page 118

Table 5: Medicines with existing equivalent in EML

Item	Form	Reason	Reference	Location
Cefotaxime	vial of 500 mg mixed with 2 ml sterile water to give 250 mg/1 ml, solution for injection IV	Equivalent in EML (ceftriaxone)	1	3.8. Page 50
Cefotaxime	vial of 1 g mixed with 4 ml sterile water	Equivalent in EML (ceftriaxone)	1	Appendix 2 Page 330
Cefotaxime	vial of 2 g mixed with 8 ml sterile water	Equivalent in EML (ceftriaxone)	1	Appendix 2 Page 330
Flucloxacillin	solution for injection, IM, IV	Equivalent in EML (cloxacillin)	1	6.9 Page 166

Table 6: Medicines where reason for discrepancy is unclear

Item	Form	Reason	Reference	Location	Action required
Parenteral					
Azlocillin	solution for injection	Recommended as example of class, second line treatment	1	6.7.3 Page 163	Could be considered for complementary list
Equine tetanus antitoxin	solution for injection, IM	Human product is listed. Is Equine still relevant?	6	F-67	Advice needed from Ana Padilla
Paraldehyde	5 ml vial, solution for injection	Recommended as second line treatment with diazepam as preferred option	1	Appendix 2 Page 342	Could be considered for complementary list but may not be available
Pralidoxime	solution for injection, IV	antidote	1	1.5.4 Page 29	Consider as part of 'review of antidotes'
Dosage form not specified					
Copper	not mentioned	Recommended as micronutrient in severely malnourished children. Might be part of multivitamin preparation	1	7.4.6 Page 183	Consider whether needed - application
Gatifloxacin	not mentioned	Option for MDR-TB; department as not recommended addition to EML	5	Annex 3, Table A3.1, Page 31	None at this time
Moxifloxacin	not mentioned	Option for MDR-TB; department as not recommended addition to EML	5	Annex 3, Table A3.1, Page 31	None at this time
Prazosin	not mentioned	Recommended only for management of pulmonary oedema in scorpion stings	1	1.7 Page 34	Unlikely to be essential medicine. Does it work?
Prothionamide	not mentioned	Option for MDR-TB; department as not recommended addition to EML	5	Annex 3, Table A3.1, Page 31	None at this time
Terizidone	not mentioned	Option for MDR-TB; department as not recommended addition to EML	5	Annex 3, Table A3.1, Page 31	None at this time

Item	Form	Reason	Reference	Location	Action required
Thioacetazone	not mentioned	Option for MDR-TB; department as not recommended addition to EML	1	Appendix 2 Page 352	None at this time
Oral and Rectal					
Duovir (3TC+ZDV)	tablets of 150 mg 3TC plus 300 mg ZDV plus	Is being considered as part of HIV Department's work	1	Appendix 2 Page 349	Application for July 2007
Paraldehyde	in arachis oil, rectally	As for parenteral	6	F-67	Could be considered for complementary list but may not be available
Pivmecillinam	200 mg tablet	Recommended as example of class as 2 nd or 3 rd line alternative	1	Appendix 2 Page 343	Could be considered
Triomune (3TC + d4T + NVP)	oral: tablets of 150 mg 3TC plus 200 mg NVP plus 30 mg d4T OR 150 mg 3TC plus 200 mg NVP plus 40 mg d4T	Is being considered as part of HIV Department's work	1	Appendix 2 Page 349	Application for July 2007
Topical					
Norfloxacin	ear drops	No ENT section	1	6.7.3 Page 163	May be part of ENT review