

# **DRAFT REPORT**

## **OF THE SECOND MEETING OF THE SUBCOMMITTEE OF THE EXPERT COMMITTEE ON THE SELECTION AND USE OF ESSENTIAL MEDICINES**

29 September to 3 October 2008

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## Members of the Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

**Mrs Jehan Mohammed Ali Al-Fannah**, Department of Pharmacy, Royal Hospital, P. O. Box 1331, Postal Code 111, CPO-Sultanate of Oman, Muscat, Sultanate of Oman. (*Vice-Chair*).

**Dr Helena Lutécia L. Coelho**, Pharmacy Department. Federal University of Ceara  
rua Capitão Francisco Pedro 1210 60431327 Fortaleza, CE, Brazil.

**Professor Noël Cranswick**, Clinical Pharmacologist, Royal Children's Hospital/APPRU  
5<sup>th</sup> Floor Main Building, Flemington Road, Parkville, Victoria, Australia 3052..

**Mr Andy Gray**, Department of Therapeutics and Medicines Management, Nelson R.  
Mandela School of Medicine, University of KwaZulu-Natal, PBag 7, Congella, Durban, 4013,  
South Africa. (*Chair*).

**Professor Prakash Mohan Jeena**, Department of Paediatrics and Child Health, Nelson R.  
Mandela School of Medicine, University of KwaZulu-Natal, Private Bag x1, Congella,  
Durban, 4013, South Africa.

**Dr Kalle Hoppu**, Director, Poison Information Centre, Helsinki University Central Hospital,  
P.O. Box 340 (Haartmaninkatu 4), 00029 HUS (Helsinki), Finland.

**Dr Peter Kazembe**, Baylor College of Medicine, Children's Clinical Centre of Excellence,  
Private Bag B-397, Lilongwe, Malawi.

**Dr Gregory L. Kearns**, Marrion Merrell Dow / Missouri Chair of Pediatric Medical Research,  
Professor of Paediatrics and Pharmacology, University of Missouri Kansas City, Chairman of  
the Department of Medical Research and Associate Chairman, Department of Pediatrics,  
Children's Mercy Hospital and Clinics, 2401 Gillham Road, Kansas City, MO 64108, USA.  
(*Rapporteur*).

**Dr Anita Zaidi**, Associate Professor, Department of Paediatrics and Microbiology, Aga Khan  
University, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan.

## Temporary Advisers

**Professor Dai Yao Hua**, Director, WHO Collaborating Center for Child Health, Capital  
Institute of Paediatrics, South Building 2, Ya Bao Road, 100020 Beijing, China.

**Dr Jacqueline Deen**, Research Scientist, c/o Joint Malaria Programme Office, Ambrela  
National Institute for Medical Research, P.O. Box 5004, Tanga, United Republic of Tanzania.

**Dr Stuart MacLeod**, Executive Director, Child & Family Research Institute, Children's &  
Women's Health Centre of British Columbia, Ambulatory Care Building, Room K4-133, 4480  
Oak Street, Vancouver, BC V6H 3V4, Canada.

**Professor Tony Nunn**, Clinical Director of Pharmacy, Royal Liverpool Children's NHS Trust, and Associate Director, Medicines for Children Research Network, University of Liverpool, Eaton Road, GB-Liverpool L12 2AP.

**Dr Robert G. Peterson**, Clinical Professor, Department of Paediatrics, University of British Columbia, Room 2H2, BC Children's Hospital, 4480 Oak Street, Vancouver, Canada.

**Dr Shalini Sri Ranganathan**, Senior Lecturer in Pharmacology & Consultant Paediatrician Department of Pharmacology, Faculty of Medicine, University of Colombo, P.O. Box 271, Kynsey Road, Colombo 8, Sri Lanka.

**Professor H. P. S. Sachdev**, Senior Consultant, Paediatrics and Clinical, Epidemiology, Sitaram Bhartia Institute of Science and Research, E- 6/12 Vasant Vihar, New Delhi 110 057, India.

**Dr Elizabeta Zisovska**, Associate Professor of Pediatrics, Chief of the Neonatal Department, Clinic for Gynecology and Obstetrics; Vice President of Perinatal Association. Vasil Glavinov Street, Number 3-6/1 1000 Skopje, Republic of Macedonia.

## Intergovernmental organizations

**Mrs Hanne Bak Pedersen**, Deputy Director, Programme, UNICEF Supply Division, UNICEF Plads 1, Copenhagen Freeport, DK-2100 Copenhagen OE.

## WHO Secretariat

Dr Hans V. Hogerzeil, Director, Essential Medicines and Pharmaceutical Policies, HSS/EMP.

Dr Clive Ondari, Coordinator, Medicines Access and Rational Use, HSS/EMP/MAR.

Dr Suzanne Hill, Scientist, Medicines Access and Rational Use (*Secretary*), HSS/EMP/MAR.

Dr Sarah Hanieh, Research Officer, Medicines Access and Rational Use, HSS/EMP/MAR.

## 1. Introduction

The WHO Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 29 September to 3 October 2008. The meeting was opened on behalf of the Director-General by Dr Hans Hogerzeil, Director OF the Department of Essential Medicines and Pharmaceutical Policies, who noted that this was the second meeting of the Subcommittee, following its original approval by the Executive Board in May 2007 (EB121.R2). He outlined the procedures of the meeting to participants, noting that the Subcommittee is not a representative one and that all members participate in their personal capacity and are not allowed to take instructions from any government or any other authority.

The WHO Secretariat requested and received agreement from the Committee to hold an open session as part of its meeting (see Section 2). The purpose of the open session was to allow all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines for Children (EMLc). For Subcommittee members it provided an opportunity to receive, at first-hand, additional information and opinion on matters under consideration. Discussions and considerations of the open session are reflected in the report of the meeting.

The full texts of the applications for changes, additions or deletions with all the evidence and references, as well as the external reviews and comments received, are not included in the report but remain available on the WHO web site, and are accessible through the Essential Medicines Library (<http://www.who.int/emlib/>).

## 2. Open session

This session of the meeting was opened by Dr Hans Hogerzeil. He welcomed external participants and noted that all comments made during the session would be noted and taken into consideration by the Expert Subcommittee when formulating their recommendations.

The Secretariat provided an update on work undertaken since the first meeting of the Subcommittee in 2007 including progress made in relation to the World Health Assembly Resolution on Better Medicines for Children. This update included highlighting the global burden of disease mortality in children under five years of age, and some of the challenges of ensuring equitable access to essential medicines in children in different countries (for example, limits on logistical capacity in isolated island countries). Progress in work on the Resolution was also described, including the assessment of availability of medicines for children in several countries, the revision of national medicines lists to include medicines for children, and the launch of an advocacy campaign, 'Make Medicines Child Size' that aims to promote the development of appropriate high quality essential medicines for children.

Participant statements were received from:

- Dr Kate Armstrong, President of CLAN (Congenital Adrenal Hyperplasia: Caring and Living as Neighbours).

- Dr Myriam Henkens, International Medical Coordinator of Médecins Sans Frontières (MSF).
- The representative for the Permanent Mission of Canada.
- Mrs Hanne Bak Pederson, UNICEF.
- Dr Rajiv Bahl WHO Department of Child and Adolescent Health and Development.

Comments were received from UNICEF, reiterating the importance of the EMLc, and the WHO Child and Adolescent Health and Development Department, which welcomed the opportunity to be involved in the Subcommittee meeting to offer its perspective on several of the applications.

In their absence, the Secretariat read the statements from Drs Armstrong and Henkens. Dr Armstrong wished to emphasize the essential and global requirement for hydrocortisone and fludrocortisone as life-saving drugs in the management of congenital adrenal hyperplasia and adrenal insufficiency, and urged their inclusion on the EMLc. MSF sent a number of comments outlining its support for the inclusion of liposomal amphotericin B, doxycycline, oral salbutamol and quinolones on the Core List, but opposing the addition of lindane. The representative of the Permanent Mission of Canada posed a question to the Subcommittee regarding the proposal for the deletion of vitamin A 50 000 IU capsule.

### 3. Review of terms of reference

The Subcommittee reviewed the terms of reference provided to it by the Executive Board, reproduced below. Discussion of the terms of reference is provided in this section of the report; amendments to the Model List of Essential Medicines for Children are discussed in Section 4.

The Executive Board:

*1. DECIDES to establish as from June 2007 a temporary Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines, of no more than 15 members, with the following terms of reference:*

- *to prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children;*
- *to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries;*
- *to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups;*

- *to identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations;*
- *to report to the Expert Committee on the Selection and Use of Essential Medicines in 2009.*

*2. FURTHER DECIDES that the temporary Subcommittee shall terminate in 2009, after its report to the Expert Committee on the Selection and Use of Essential Medicines."*

The Subcommittee evaluated its progress based upon the terms of reference given to it by the Executive Board. A summary of progress for each of the terms of reference is provided as follows:

**Term of reference 1** – *prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children*

Through review and deliberations, the Subcommittee substantially increased and refined the information contained in the EMLc over what had been presented and approved in 2007. The proposed second WHO Model List of Essential Medicines for Children is provided as Annex<sup>o</sup> 2 to this report, for the Expert Committee to review and approve at its next meeting. Further discussion of this List is found below, under term of reference 5.

In spite of these accomplishments, work remains incomplete, largely due to the volume of information necessary to construct an EMLc that will meet the needs of the world's children. During its deliberations, the Subcommittee worked diligently to identify gaps dealing with a wide range of information (clinical pharmacology and therapeutics, clinical toxicology, pharmacovigilance) associated with medicine products, their availability in formulations suitable for children in both developed and developing nations, and their suitability for use in children. The decisions reached and recommendations made by the Subcommittee were largely driven by considerations of therapeutic decision/making as opposed to generating lists of specific products. Decisions were based on review of available accumulated evidence whenever possible as opposed to current practice. The Subcommittee recognizes that when data are not available from paediatric clinical trials, there is still an imperative to make decisions on the available information as it is unethical to deprive children of access to necessary treatment.

**Term of reference 2** – *to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries*

Comments were received by the Subcommittee from Dr Sabine Kopp representing the WHO Expert Committee on Specifications for Pharmaceutical Preparations, who discussed the development of a working paper entitled 'Development of Paediatric Medicines: Pharmaceutical Development, Points to Consider'. A number of drafts have already been prepared and revised, following several comments that had been received. It was also noted that an informal working group has been established in collaboration with the National Institute of Child Health and Human Development, National Institutes of Health, USA, and

others to ensure that the ongoing work of the Subcommittee satisfies the above terms of reference, particularly with regard to determining suitability criteria for dosage forms of medicines for children.

During its review of the EMLc, the Subcommittee identified a list of adult preparations that are frequently prepared extemporaneously for administration to children (Table 1). The Subcommittee recommends development of a set of guidelines on the use of extemporaneous preparations in children, including highlighting those medicines (not listed) that should never be prepared in an extemporaneous manner.

**Table 1. Common extemporaneous preparations**

Medicine	Existing form	Extemporaneous preparation
Acetic acid	Ear drops	Compounded
Anti-neoplastic medicines	Various	Preparation of lower dose forms or forms for alternative routes of administration
Artemether + lumefantrine	Tablet	Crushed tablet
Ethambutol	Tablet	Crushed for oral liquid
Fluconazole	Capsule	Opened for administration as liquid
Fludrocortisone	Tablet	Administered as liquid
Gentamicin	Eye drop	Combined with injection for higher strength
Hydrochlorothiazide	Tablet	Administered as liquid
Hydrocortisone	Tablet	Administered as liquid
Isoniazid	Liquid form	Administered rectally
Levothyroxine, propylthiouracil	Tablet	Administered as liquid
Midazolam	Injection	Administered as oral liquid
Morphine	Oral, injection	Preparation of liquids, dilution of injection
Peritoneal dialysis	Various	Preparation of different strengths/formulations
Prostaglandins	Injection	Administered as liquid
Pyridostigmine	Tablet	Administered as liquid
Pyridoxine	Tablet	Administered as liquid
Sulfadoxine + pyrimethamine	Tablet	Crushed for liquid
Thiamine	Tablet	Administered as liquid

This report of the Subcommittee clearly reflects that work addressing suitability criteria for dosage forms is underway but is still far from complete. It was noted that specific recommendations for additions or amendments to the List were driven in large part by products that were identified as available in highly developed countries, with the assumption that they would be adopted and/or readily accepted for procurement or manufacture by developing countries. The Subcommittee also identified significant information gaps and research issues related to further development of dosage forms. In the absence of a mandate or mechanism for the Subcommittee to take the next steps to address these challenges, its recommendations must be considered, at this juncture, as suggestions for continued work by WHO.

**Term of reference 3** – *to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups*

As regards this term of reference, the Subcommittee has achieved only a conceptual beginning. Recommendations provided reflect expert opinion offered in the hope of providing direction to WHO that would enable it to leverage resources required to ensure that appropriate paediatric medicine products are formulated and made broadly available. When possible, specific recommendations for formulations were made (e.g. concentrations of drugs in parenteral solutions appropriate for use in neonates and young infants). The Subcommittee emphatically supports the need to address rational therapeutic use of these formulations and also, careful and critical assessment of their efficacy and safety. Furthermore, considerations of product safety must take into account not only the active ingredients but also excipients that may have intrinsic pharmacologic activity.

**Term of reference 4** – *to identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations*

The Subcommittee identified and prioritized clinical research and information gaps related to paediatric therapeutics, ranging from product availability to considerations of medicine selection and therapeutic use. Specific recommendations are provided in Boxes 1-4.

Box 1 lists areas in paediatric therapeutics where more information is clearly needed in order to consider further expansion of the EMLc so that the need for additional medicines required by children can be met. Specific recommendations for systematic reviews and evidence syntheses to be conducted and then evaluated by the Subcommittee/Expert Committee are listed with relative priority designated (H - high; M - medium and L - low). These are generally listed in the order of the sections of the List.

**Box 1. Evidence syntheses/systematic reviews required**

1. Appropriate medicines for pre-operative use in children H
2. Appropriate medicines for use in short/term procedures (conscious sedation) in children H
3. Review use of methylene blue in children M
4. Review use of oral iron/lead chelators M
5. Appropriate medicines for use in resuscitation in children H
6. Essential medicines for pain management in children H
7. Essential medicines for management of neuropathic pain in children including the role of lamotrigine, amitriptyline and gabapentin H
8. Essential medicines for management of juvenile inflammatory arthritis L
9. Review of safety and effectiveness of penicillamine compared to sodium calcium edentate L
10. Review of safety and effectiveness of antihelmintics in children H
11. Antimonials as essential medicines for leishmaniasis (core /complementary) H
12. Safety and efficacy of streptomycin in childhood TB H
13. Other questions identified in the report on TB medicines H
14. Essential cytotoxic therapies for the commonest tumours in childhood M
15. Review of safety/toxicity of gentian violet L
16. Safety of topical antibiotics including tetracycline ointment in neonates H
17. Alternatives to benzyl benzoate for scabies treatment in young children M
18. Identification of essential diagnostic (contrast) agents for use in children L
19. Essential diuretics for use in children H
20. Clinical use of ondansetron in children M
21. Choice and optimal use of laxatives in children H
22. Essential medicines for treatment of mental health conditions in children H
23. Identification of essential vitamin and mineral supplements (including iron and folic acid) especially in HIV/TB/malnutrition H
24. Review role of leukotriene antagonists in management of childhood allergic rhinitis L

In identifying necessary priorities for immediate action, the Subcommittee concluded that there were several areas where existing data were available and could easily be formulated into proposals for consideration of addition to the EMLc. Specific recommendations for such action are summarized in Box 2 below.

### **Box 2. Examples of areas where data exist and applications could be immediately developed**

1. Application for a non-sedating antihistamine for children (appropriate comparisons)
2. Application for heat stable protease inhibitors (LOP/RIT) for HIV management
3. Assess 2 new clinical trials on safety and efficacy of procaine penicillin in neonates
4. Comparison of sulfadiazine and co-trimoxazole in treatment of toxoplasmosis (possible deletion of sulfadiazine)
5. Review of liposomal amphotericin B as treatment of fungal infections in children H
6. Applications for amiodarone, lignocaine and adenosine in children
7. Application for glucagon
8. Development of child-friendly equipment for medicine administration sizes for all ages

Discussion emanating from the meeting of the Subcommittee revealed that there were unanswered questions arising from each application. It was also considered likely that the evidence syntheses/systematic reviews listed in Box 1 will produce additional research questions. These information gaps will require the conduct of specific research targeted to critical areas in paediatric therapeutics. A listing of highlighted research issues identified during both meetings of the Subcommittee and the research consultation held in October 2007 is contained in Box 3 below.

### **Box 3. Research gaps**

1. Safety and efficacy of meropenem in neonates
2. Safety and efficacy of protease inhibitors in children with weights less than 10 kg
3. The use of rifabutin and rifapentine for children with TB co-infection in HIV
4. The role of pharmacotherapy, including amitriptyline, lamotrigine and gabapentin, in neuropathic pain management
5. Research on international controls over medicines used in palliative care and the need to allow better access in situations of medical need, including use in children
6. Research on malaria treatments, including FDCs that are appropriate for children
7. Research on treatments for Chagas disease - need for safer treatment
8. Research on access to insulin
9. Research on supply chain issues relevant to the EMLc
10. Research on delayed adverse effects, especially effects on development
11. Research on factors that modify dose-response relationships in individuals and populations

In developing the updated EMLc, the Subcommittee identified the following specific products (Box 4) as being potentially useful for treatment of children. This is, however, not to be considered as a complete or exhaustive list as it is anticipated that in future deliberations of the Expert Committee that additional paediatric products will be identified.

**Box 4. Product gaps**

1. Boosted heat-stable protease inhibitor FDCs based on existing products and appropriate dosage forms (e.g. sprinkles)
2. Inhaled beta-agonists and corticosteroids
  - a. smaller packaging
  - b. affordable canisters
3. Prostaglandin E oral formulation
4. Amphotericin B - appropriate strength for neonates
5. Appropriate insulin dosage forms for neonates
6. Appropriate strength oral and injectable morphine formulation for neonates
7. Oral liquid form of hydrocortisone
8. Mefloquine liquid formulation
9. Pyrimethamine liquid formulation
10. Chlorhexidine digluconate 7.1%
11. Phenobarbital sodium solution - appropriate strength and alcohol-free formulation
12. A multivitamin preparation suitable for general use in neonates and young children
13. An accessible, palatable and affordable preparation of zinc salts

As with the issues of paediatric formulations, the guidance given to the Secretariat regarding research priorities is, at present, directional as opposed to strategic. The Subcommittee further identified that for these clinical information and research gaps to be adequately addressed, it will be required that areas of expertise represented by the current Subcommittee have an effective and dynamic interface with working groups at WHO that are charged with developing treatment guidelines. Proof-of-concept for the utility of such an approach was offered by the example of recent efforts to address the development of a suitable fixed-dose formulation containing three drugs identified as standards of care for the treatment of tuberculosis in infants and children in the developing world.

**Term of reference 5** – *to report to the Expert Committee on the Selection and Use of Essential Medicines in 2009*

The Subcommittee is pleased to report that significant progress has been made in the further development of the EMLc. The list has increased definition and expanded content driven by the assessment of objective evidence. Two new sections are recommended: medicines for ear, nose and throat disease and medicines specifically for neonatal care. The first of these sections includes topical preparations needed for the management of ear, nose and throat disorders, conditions which occur very commonly in children throughout the world and cause significant morbidity, that were not included elsewhere in the EMLc.

In recognition of the high burden of disease occurring in neonates and young infants, the Subcommittee considered the preparation of an essential medicines list for neonates. The Subcommittee proposes to add a section to the EMLc that specifies medicines that are uniquely required for the treatment of neonates. An annex of medicines from the EMLc that were felt to be essential in treating a variety of neonatal conditions was also provided. In addition, medicines have also been proposed for inclusion under the heading of palliative care.

Appropriate utilization of medicines on the EMLc will require purposeful and careful coordination with WHO programmes engaged in the development of treatment guidelines for children. This recommendation is offered as a direct result of the Subcommittee being aware that there are existing treatment guidelines which are not aligned with the best available evidence.<sup>1</sup> It is the contention of the Subcommittee that the EMLc can and must be used to support the continued development of paediatric-specific treatment guidelines for a variety of conditions and diseases. The Subcommittee also asserts that it is critical that the work undertaken thus far continue. Specifically, WHO should undertake a comprehensive, translational approach towards paediatric therapeutics which focuses clearly on medicine use and the assessment of safety and efficacy associated with drug treatment. To attain this goal for the benefit of children across the world will require continuity of effort, widened engagement of professionals with paediatric expertise that spans the continuum of drug therapy (e.g. formulation development, drug delivery, clinical pharmacology, paediatric medicine) and adoption of a strategy that continues to place a priority on the value of providing children in all countries with the right of a healthy life.

Finally, the Subcommittee discussed the most effective and efficient mechanism to provide the continuity and level of engagement required to achieve the aforementioned objectives.

To this end, the following recommendations are offered to the Expert Committee for consideration:

1. This report of the Subcommittee will be tendered to the Expert Committee for consideration, deliberation and adoption at the meeting to be held in March 2009.
2. In the foreseeable future, it is essential that the EMLc remain separate from the WHO Model EML in order to maintain a critical focus on the needs of children.
3. The Secretariat should utilize available resources necessary to undertake reviews recommended by the Subcommittee and also to address information and research gaps of high priority for the paediatric medicines initiative. This may be done through the development of specific contracts and/or the establishment of strategic working groups that might be focused on a specific issue.
4. Consideration should be given to the appropriate constitution of future Expert Committees in order to meet the demands of United Nations Millennium Goals 4 and 6 to focus on paediatric priorities and Resolution WHA60.20. This would include further development and expansion of the EMLc and establishing plans for its continued maintenance.
5. To meet the critical needs of improving paediatric therapeutics throughout the world through an evidence-based approach, it is imperative that WHO continue to work effectively to define and address research gaps. Most importantly, WHO should create approaches to generate the new knowledge necessary for translation of discovery into rational therapeutic practices.

## 4. The WHO Model List of Essential Medicines for Children - by section

### Section 4. Antidotes and other substances used in poisonings

Section 4 of the Model List of Essential Medicines concerns medicines used as antidotes and for the management of poisonings. The Subcommittee had requested further evaluation of the burden of disease and disability in children due to poisoning as well as applications for specific antidotes deemed critical for children. The Secretariat had therefore commissioned reviews of two key antidotes already on the List and the preparation of an application for inclusion of pralidoxime.

Comments were received from the South Asian Clinical Toxicology Research Collaboration and the WHO Department of Protection of the Human Environment.

#### 4.1 *Non-specific*

##### **Charcoal, activated (Review)**

###### *Core List*

The Subcommittee considered the review of activated charcoal for the treatment of non-specific poisoning in children. The review was commissioned by the Secretariat and provided by Dr Jennifer A. Lowry from the University of Missouri-Kansas City and Children's Mercy Hospital. Expert review comments were provided by Dr Helena L. Coelho and Professor N. Cranswick.

Accidental poisonings in children are a significant problem, particularly throughout the developing world. The Subcommittee noted that there is a paucity of high quality evidence for the efficacy of activated charcoal in children, and that the majority of the literature is based on a collection of case series and case reports in adult patients. Position statements from the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists were reviewed that suggested that activated charcoal is most effective when given within the first one hour following the ingestion of a poison, and that multi-dose activated charcoal should only be used following specific ingestions. Comments were also considered from the South Asia Clinical Toxicology Collaboration who supported the inclusion of activated charcoal in the List.

The Subcommittee considered that despite the limited evidence from controlled clinical trials for the efficacy of activated charcoal in children, when considered on balance with the low risk of adverse reactions and the limited alternatives for gastric decontamination, activated charcoal should remain on the List.

## 4.2 Specific

### Acetylcysteine (Review)

The Subcommittee reviewed the inclusion of N-acetylcysteine (NAC) on the List as an antidote for paracetamol (acetaminophen) toxicity. A systematic review was commissioned by the Secretariat and provided by Dr D. Adam Algren from the University of Missouri-Kansas City and Children's Mercy Hospital. The expert comments were provided by Mrs Jenna Mohammed Ali Al-Fannah and Dr Helena L. Coelho. Comments were noted from members of the South Asian Clinical Toxicology Research Collaboration who supported the inclusion of oral NAC on the List.

The review summarized the clinical evidence for use of NAC in adults and noted that no randomized efficacy trials have been conducted in children. There is significant clinical evidence in adult populations to suggest that oral and intravenous NAC are equally effective. The intravenous form of NAC can also be administered orally. A small study involving 25 paediatric patients demonstrated comparable efficacy between IV and oral NAC. Several observational studies involving the use of oral NAC showed a decrease in the incidence of hepatotoxicity in those patients who had NAC therapy initiated within 10 hours of ingestion. However these studies involved only small numbers of paediatric patients.

The Subcommittee noted that the major point with regard to adverse effects in children is that intravenous infusion in children may be associated with hyponatraemia if excessive fluids are administered in conjunction with NAC and also, anaphylactoid reactions are associated with the parenteral formulation.

The Subcommittee agreed that NAC is considered the treatment of choice for paracetamol toxicity where dose and/or paracetamol plasma concentrations would suggest the risk of serious hepatotoxicity from an acute ingestion. It was agreed that IV NAC remain on the List, and that the oral form be added. The proposed WHO Model Formulary for Children may need to contain advice on appropriate use, including guidance on initiation of therapy and avoidance of unnecessary administration in the situation of sub-toxic doses of paracetamol.

### Pralidoxime (Inclusion):

#### *Core List*

The Subcommittee considered the proposal for inclusion of pralidoxime for the treatment of organophosphate poisoning in children. Expert comments were provided by Professor H.P.S. Sachdev. Atropine is currently the only antidote on the List for acute organophosphate poisoning.

The Subcommittee noted that information on the prevalence of acute organophosphate poisoning in children is limited, although it is known to be an increasing problem worldwide, particularly in rural regions of developing countries.

The Subcommittee considered the evidence for the safety and efficacy of pralidoxime provided in the proposal. The proposal was based on five systematic reviews of studies involving adult patients.<sup>2,3,4,5,6</sup> There were no data in these reviews which described the use of pralidoxime in children. The study designs were of variable quality. Collectively, the data from the adult studies were unable to conclusively establish the effectiveness of pralidoxime in the treatment of organophosphate poisoning. The Subcommittee was made aware of two case series describing the use of intravenous pralidoxime in children with organophosphate poisoning.<sup>7,8</sup>

Comments from the South Asia Clinical Toxicology Collaboration, involved in a large randomized controlled trial of pralidoxime in Sri Lanka, were noted: the Collaboration stated that data analysed thus far did not provide supporting evidence for the inclusion of pralidoxime in the List.

The Subcommittee considered that at this time there was insufficient evidence to justify the inclusion of pralidoxime on the EMLc. It recommended that new trial data and the additional paediatric data be considered in March 2009.

For further revision of this section, the Subcommittee recommends the future consideration of additional iron and lead chelating agents and methylene blue as potential essential antidotes for paediatric use.

## **Section 6. Anti-infective medicines**

At its first meeting in July 2007 the Subcommittee identified a number of questions about anti-infective medicines for children that needed further review. These included the need to obtain additional evidence and safety about products already on the List as well as applications for new products.

### **6.2 Antibacterials**

#### **6.2.1 Beta Lactam medicines**

The Subcommittee considered reviews of efficacy and safety for procaine benzylpenicillin, cefatazidime and ceftriaxone, the carbapenems as a class, and a new application for cefalexin.

Expert comments on the proposals were prepared by Mr Andy Gray, Dr Kalle Hoppu, Professor Prakash Mohan Jeena, Dr Peter Kazembe, Professor Harshi Sachdev, Drs Anita Zaidi and Elizabeta Zisovska.

Comments were received from the WHO Department of Child and Adolescent Health and Development.

#### **Cefalexin (Inclusion)**

A new proposal, commissioned by the Secretariat, for the inclusion of cefalexin on the List was considered. Expert comments for cefalexin were provided by Mr Andy Gray

and Dr Kalle Hoppu. It was noted that the WHO Department of Child and Adolescent Health and Development suggested inclusion on the Complementary List.

The Subcommittee noted that the Expert Committee had previously considered an application for the addition of cefazolin and cefalexin in March 2007. At that time, cefazolin was added to the List based on the high quality clinical evidence for its use in surgical prophylaxis. The proposal for cefalexin, on the other hand, was rejected on the basis of limited evidence for its comparative effectiveness versus other antibiotics already included on the List, and concerns about inappropriate prescribing.

The new proposal stated that first generation oral cephalosporins are generally inexpensive, easy to administer and commonly used in community outpatient settings. They provide good cover against the common organisms (e.g. *Staphylococcus aureus* and *Streptococci*) that cause uncomplicated community-acquired respiratory, skin and soft tissue infections, however evidence for *superiority* over other antibiotics is limited.

The Subcommittee noted that evidence for clinical efficacy and safety of cefalexin in children was limited. Evidence presented in the proposal included a Cochrane systematic review<sup>9</sup> of 16 studies for the treatment of impetigo, that included both children and adult patients. Other trials<sup>10,11</sup> using cefalexin in children and adolescents for treatment of Group A streptococcal pharyngitis showed equivalent clinical cure rates between cefalexin and penicillin. The efficacy of cefalexin in the treatment of urinary tract infections without proven culture sensitivity has not been demonstrated, and there are insufficient data available on the use of cefalexin for prevention of rheumatic fever or carditis.

After considerable deliberations, the Subcommittee found potential merits associated with the availability of cefalexin. These included evidence of effective treatment of skin and soft tissue infections produced by a variety of pathogens (with the exception of methicillin-resistant *Staph aureus*), the treatment of uncomplicated urinary tract infections produced by sensitive pathogens, and the perception that better palatability is associated with improved adherence in treatment regimens, particularly for prolonged treatment such as in the case of osteomyelitis. Also, it was recognized that cefalexin can often be safely administered to patients who demonstrate hypersensitivity reactions to penicillin. The Subcommittee therefore added cefalexin to the EMLc Core List.

### **Procaine benzylpenicillin (Review)**

The Subcommittee considered the review of procaine benzylpenicillin in neonates. The Subcommittee had previously raised concerns in October 2007 about its safety and efficacy in neonates, despite its widespread use in this age group. Expert reviews were provided by Drs Stuart MacLeod and Gregory Kearns.

It was noted that (crystalline) benzylpenicillin is the preferred agent for serious infections such as neonatal sepsis and congenital syphilis, however several guidelines

(American Academy of Pediatrics, CDC Sexually Transmitted Diseases Treatment Guidelines) recommend intramuscular procaine benzylpenicillin as an alternative for use in the management of proven congenital syphilis. Only one randomized controlled trial demonstrating a significant reduction in RPR titres, following treatment for congenital syphilis with either procaine benzylpenicillin or benzathine benzylpenicillin, was included in the review.<sup>12</sup>

The Subcommittee noted that although the WHO Pocket Book of Hospital Care for Children recommends intramuscular procaine benzylpenicillin in combination with gentamicin as an alternative treatment to (crystalline) benzylpenicillin for the management of neonatal sepsis and meningitis in neonates, there is no evidence for the efficacy of procaine benzylpenicillin in the management of early onset Group B sepsis, or in the community management of sepsis and pneumonia in neonates. It was also noted that procaine benzylpenicillin has low CSF penetration and therefore, may be ineffective in treating infants who develop, or who are at risk of developing, bacterial meningitis. However, the Subcommittee also noted that procaine benzylpenicillin has been used as an alternative to (crystalline) benzylpenicillin as it can easily be administered in the community with once daily intramuscular dosing.

The Subcommittee took account of the safety concerns regarding the intramuscular administration of procaine benzylpenicillin in premature and low birth weight infants, with reports of injection site abscesses, muscle fibrosis and atrophy following intramuscular injection, particularly in premature and low birth weight neonates.

Notwithstanding justifiable reservations regarding the use of procaine benzylpenicillin in young infants, the Subcommittee agreed to endorse the listing of procaine benzylpenicillin as essential without age restriction. Its use in neonates should be avoided unless intravenous administration of (crystalline) benzylpenicillin is not possible. Therefore, the Subcommittee added a note to this effect on the List. The Subcommittee noted that current studies of procaine benzylpenicillin given in combination with gentamicin as first-line treatment for infants with gram-positive infections are underway and the results will be considered when available.

### **Ceftazidime (Review)**

#### ***Complementary List***

The Subcommittee reviewed the inclusion of ceftazidime on the complementary List. Expert comments were provided by Professor Prakash Mohan Jeena. In July 2007, the Subcommittee had previously identified the need to determine whether there were preferred alternatives for use in children.

It was noted that the review found limited evidence on efficacy and safety of use of ceftazidime in children and similarly limited information about the treatment of *P. aeruginosa* in children. The main source of information was a systematic review of 57 trials comparing cefepime with other antibiotics, but only two of these trials compared ceftazidime to cefepime in children and one was in patients with febrile neutropenia, the other in patients with urinary tract infections.<sup>13</sup>

The Subcommittee noted that there was no clinical evidence for the superiority of one antibiotic over the other for the treatment of *P.aeruginosa* in cystic fibrosis, or as empirical treatment for ventilator assisted pneumonia, and that ceftazidime was the antibiotic of choice in the treatment of *B.cepacia* infections in cystic fibrosis and *B.pseudomallei* infections.

The Subcommittee also noted that there are no recommended age restrictions with ceftazidime, and that it is the least expensive of the anti-pseudomonal antibiotics according to the International Drug Price Indicator Guide.

The Subcommittee agreed that although there was no evidence to support the superior efficacy or safety of ceftazidime over other antibiotics with a similar antibacterial spectrum, the drug should remain on the Complementary List.

### Ceftriaxone

In response to safety issues raised at the First Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines in 2007, the Secretariat commissioned a review of use and safety of ceftriaxone in neonates. Expert comments were provided by Professor H.P.S. Sachdev and Dr Elizabeta Zisovska.

The review identified four trials studying use of ceftriaxone in neonates, for sepsis and meningitis. The review noted that ceftriaxone can cause significant adverse reactions in neonates, including: a potentially fatal interaction with calcium; superinfections with candida and non-susceptible bacteria like extended spectrum beta-lactamase producers; and kernicterus.

The Subcommittee considered whether the use of ceftriaxone should be contraindicated in premature infants younger than 41 weeks total age and the use restricted to infants  $\geq 1$  month of age. The Subcommittee noted that safety warnings had been issued by several regulatory authorities and Roche regarding interactions between ceftriaxone and calcium. Therefore, due to precipitation that can produce severe adverse effects, the administration of calcium and ceftriaxone in the same or different infusion lines or sites must be avoided. While current information suggests that a 48-hour period between administration of ceftriaxone and calcium is required, altered pharmacokinetics of the drug in neonates may require an even greater period of separating the administration of the two drugs. Ceftriaxone use should be avoided in neonates with hyperbilirubinemia consequent to potential disruption in bilirubin protein binding and the production of biliary sludging.

The Subcommittee recognized that a minimum age restriction was required for this medicine and therefore recommended that a note be inserted in the List to restrict use to above 41 weeks corrected gestational age. The use of ceftriaxone should be restricted to those who are being discharged from hospital who still require parenteral antimicrobial treatment and will not be receiving concomitant calcium treatment.

The Subcommittee also considered whether the medicine should be moved to the Complementary List, but on balance, decided to retain it in the Core List because of the importance of rapid treatment for meningitis at first-line health-care facilities. Given the significant safety concerns associated with the use of this medicine in neonates, it was recommended that the Advisory Committee on Safety of Medicines evaluate the use of ceftriaxone in infants and children at its next meeting.

### **Carbapenems (Review)**

#### *Complementary List*

The Subcommittee considered the review of carbapenems which was commissioned following the 2007 meeting, to identify potential alternatives to the currently listed imipenem–cilastatin. Expert comments were provided by Dr Anita Zaidi.

The Subcommittee noted that the majority of evidence for the safety and efficacy of meropenem and imipenem–cilastatin comes from a systematic review of studies in adults, which demonstrated that meropenem produced a marginally better clinical and bacteriological cure rate compared to imipenem.<sup>14</sup> The limited evidence from studies in children suggested that the efficacy and safety of meropenem and imipenem–cilastatin were comparable for most indications other than meningitis.<sup>15</sup> The Subcommittee noted that meropenem was the only carbapenem that could be used for meningitis, due to its low propensity to cause seizures even at high doses. Imipenem–cilastatin is contraindicated for meningitis.

Although the cost of meropenem is higher than that of comparators, the Subcommittee took into account that studies done in the Russian Federation, the UK, and the USA have shown that the overall cost of therapy for patients with severe infection in intensive care units is lower for meropenem when compared to imipenem–cilastatin and conventional combination antibacterial therapy.<sup>16</sup>

The Subcommittee considered that meropenem is not currently licensed for neonates. While the BNF for Children 2008 does give dosages for meropenem in neonates, these recommendations do not appear presently to be firmly supported by data from controlled clinical trials of pharmacokinetics or drug safety in this sub-population. Imipenem–cilastatin is the only carbapenem currently approved by regulatory authorities in all age groups.

The Subcommittee recommended that for all infections caused by drug-resistant pathogens known or believed to be sensitive to a carbapenem, meropenem can be considered as an alternative to imipenem–cilastatin. Given its association with the production of seizures, imipenem–cilastatin is contraindicated for use in infants and children with meningitis. In such situations, meropenem is the preferable agent. Until complete data on meropenem in young infants and neonates are available, it is recommended that imipenem–cilastatin be retained on the EMLc but a note inserted to recommend the use of meropenem where appropriate.

## 6.2.2 Other antibacterials

### Macrolides

At the Subcommittee meeting in July 2007, the question of differences in efficacy and safety between the macrolides, particularly with regard to their use in neonates, was raised. It was also noted that, with the exception of the treatment of trachoma, there was no evidence for the superiority of azithromycin over other macrolides or beta lactams. It was therefore decided that azithromycin should remain restricted to the specified indication of trachoma and that a review should be commissioned by the Secretariat to summarize the evidence regarding the use of macrolides in children, with particular regard to safety and efficacy in neonates. Azithromycin and erythromycin are the only macrolides currently on the List.

Expert review comments were provided by Mrs Jehan Mohammed Ali Al-Fannah and Dr Jacqueline Deen.

#### Comparative evidence for efficacy

There is no evidence for the superiority of azithromycin over other macrolides for the treatment of *Bordetella pertussis* or *Campylobacter jejuni*, however guidelines from the American Academy of Paediatrics and the CDC recommend azithromycin as the preferred macrolide for treatment of *Bordetella pertussis* infections. Azithromycin is the macrolide of choice for trachoma treatment in children over six months, and the efficacy of azithromycin for the treatment of trachoma has been demonstrated in several randomized controlled trials identified in the review. This is consistent with the current recommendation in WHO guidelines.<sup>17</sup>

A Cochrane review<sup>18</sup> did not find any evidence for the superiority of azithromycin in the treatment of community-acquired pneumonia over other antibiotics such as amoxicillin-clavulanic acid or erythromycin. There is no evidence that azithromycin is superior to other antibiotics for the treatment of Legionnaires' disease, acute otitis media or sinusitis.

Clarithromycin is recommended for the treatment and prophylaxis of disseminated *Mycobacterium avium intracellulare* infection in HIV infected children according to the US Centre for Disease Control guidelines. However data on the use of clarithromycin in children are scanty and it is not recommended for this indication in children aged under 20 months. It may also be effective for the treatment of pertussis, Legionnaires' disease, and *H. pylori* but there is no evidence for its superiority over the other macrolides.

#### Comparative evidence for safety

Erythromycin is administered 3 or 4 times per day. Azithromycin is administered as a single daily dose. Adverse events reported for erythromycin may include epigastric distress, hepatic dysfunction, drug interactions and in neonates, infantile hypertrophic pyloric stenosis (IHPS) that may be dose-dependent, and occurs at a rate of between 5-10%. For this reason other macrolides have often been recommended for use in neonates despite the absence of strong evidence for their safety or efficacy in this age group.

Intravenous use of erythromycin has been associated with thrombophlebitis, cardiac arrhythmias, and auditory impairment. There are no systematic reviews comparing the tolerability of erythromycin with other macrolides.

The Secretariat identified four trials directly comparing azithromycin with erythromycin *and* reporting adverse effects: two from the Cochrane review of antibiotics for community-acquired pneumonia in children,<sup>19,20</sup> one from the Cochrane review of antibiotics for pertussis<sup>21</sup> and a fourth trial (Langley et al.,<sup>22</sup> not included in either review), by far the largest direct comparison of azithromycin with erythromycin in the treatment of pertussis in 477 children.

As reported in the study by Langley et al., clinical and bacterial efficacy of the two treatments was the same. However gastrointestinal events were reported significantly more frequently in the erythromycin group (41.2%) compared to the azithromycin group (18.8%). Children randomized to azithromycin were also much more likely to have complied with antimicrobial therapy during the treatment period (90% versus 55%).

Only one study directly comparing clarithromycin with erythromycin was found,<sup>23</sup> in which clarithromycin was shown to have significantly fewer adverse events (34/76) than with erythromycin (48/77,  $P = 0.035$ ).

#### Comparative evidence in neonates

Erythromycin has been approved for use in neonates in the treatment of eye infections and pneumonia caused by *C. trachomatis*.

Azithromycin has not been approved for use in children under six months old, and evidence for its efficacy and safety is limited to a single study of 13 neonates which found azithromycin to be effective and safe in this age group. Guidelines from the CDC and American Academy of Paediatrics recommend the use of azithromycin in children under one month for the treatment of *Bordetella pertussis* infections.

Clarithromycin is not licensed nor recommended for use in neonates.

Currently, the cost of azithromycin is US\$ 0.53/DDD, compared to erythromycin US\$ 0.10/DDD and clarithromycin US\$ 0.44/DDD for solid dosage forms based on the Management Sciences for Health International Drug Price Indicator Guide.

The Subcommittee noted that:

1. Azithromycin remains the antibiotic of choice for the treatment of trachoma.
2. The drug interaction profile for the macrolides differs with erythromycin and clarithromycin producing inhibition of CYP3A activity sufficient to alter the pharmacokinetics of drugs that are CYP3A4/5 substrates. Azithromycin appears to be devoid of drug interactions with CYP3A substrates.

3. There remains limited evidence for the superiority of one macrolide over the other in the management of other infections. They are best considered as clinically interchangeable in terms of efficacy.
4. There is minimal data on the comparative safety of the macrolides. Azithromycin is favoured but this is not clinically significant.
5. Efficacy and safety of macrolides in children under six months is primarily for erythromycin; data for azithromycin and clarithromycin in children less than six months is scanty. Despite this lack of quality evidence, guidelines from the CDC and American Academy of Paediatric guidelines continue to recommend the use of azithromycin in children in this age group for the treatment and prophylaxis of *Bordetella pertussis*, as azithromycin may be better tolerated and easier to administer. There is the potential for resistance to develop if azithromycin is overused, or used inappropriately.

It was therefore agreed that azithromycin remain on the EMLc with a note regarding its appropriate indication, that oral erythromycin be retained but without annotation and that intravenous erythromycin be deleted.

### **Fluoroquinolones (Review)**

In 2007, the Subcommittee reviewed the listing of fluoroquinolones for use in children and given concerns about the potential for the over/inappropriate use of fluoroquinolones outside of the recommended indications, a review on the efficacy, safety and rational use of fluoroquinolones in children was requested. Expert comments were provided by Professor Dai Yao Hua and Dr Jacqueline Deen.

The review commissioned by the Secretariat cited a Cochrane review of quinolones for treatment of typhoid fever,<sup>24</sup> in which three trials were exclusively in children (comparisons were of ofloxacin with cefixime, norfloxacin with ceftriaxone, and ofloxacin for two versus three days). The overall conclusion of the Cochrane review was that there was no evidence for superiority of quinolones in the treatment of typhoid fever in children over other antibiotics such as ceftriaxone or cefixime.

It was noted that evidence for the use of oral ciprofloxacin in the management of shigella, salmonella and other gastrointestinal infections consists mostly of case series and case reports. The Zimbabwe, Bangladesh, South Africa Study group has conducted a multicentred double-blind randomized controlled trial<sup>25</sup> in which 235 children with shigella were randomized to receive oral ciprofloxacin for a three- or five-day course. All children were microbiologically cured and all isolates were sensitive to ciprofloxacin. Several countries have recently reported increased resistance to fluoroquinolones in the management of these conditions.

No randomized controlled trials evaluating efficacy of a fluoroquinolone in the management of meningitis in children were identified, and clinical efficacy of fluoroquinolones in neonates and pre-term infants is scanty. An additional search of the literature undertaken by the Secretariat identified two further studies not

included in the review: a matched case-control study<sup>26</sup> in which 30 neonates were treated with parenteral ciprofloxacin for 14 days. When controlled for birth weight and gestation, cartilage size was not affected by ciprofloxacin. The second, a prospective long-term follow up study carried out in Bangladesh,<sup>27</sup> and involving 48 preterm infants less than 33 weeks gestation concluded that ciprofloxacin was a safe therapeutic option for newborns with sepsis produced by multi-resistant organisms, with no differences in growth and development observed in the ciprofloxacin group during treatment or follow up.

It was noted that there are no data comparing the superiority of the other quinolones such as gatifloxacin and moxifloxacin over ciprofloxacin in children.

The application included a review of the findings in animals and compared this to a summary of findings in children (31 reports, > 7000 children) where arthropathy was found to be reversible, without long-term sequelae, and not convincingly correlated with the use of fluoroquinolones in children. The Subcommittee noted the recent warnings issued by the FDA about the risk of arthropathy in adult patients > 65 years and the risk of tendon rupture associated with protracted treatment in adults > 60 years of age.

The Subcommittee agreed that:

- evidence for the clinical efficacy and superiority of fluoroquinolones over other antibiotics in children is limited, particularly within the neonatal and preterm period;
- ciprofloxacin remains the fluoroquinolone with the most evidence for use and safety in children;
- inappropriate use of fluoroquinolones has the potential to rapidly increase the emergence of resistance.

The Subcommittee concluded that sufficient evidence is available that supports the use of ciprofloxacin as a second-line treatment for specific, severe infections in paediatric patients. Given patterns of use, it was decided that ciprofloxacin should remain the only fluoroquinolone on the List as there is evidence for ciprofloxacin to be used in other infections. The statement regarding *Shigella* should be deleted. It was also recommended that the safety issues pertaining to fluoroquinolone use in neonates and children be considered by the Advisory Committee on the Safety of Medicines at its next meeting.

### **Tetracycline (Review)**

The use of tetracyclines in children was reviewed by the Subcommittee. The inclusion of tetracycline on the List for use in severe cholera had previously been reviewed by the Subcommittee in July 2007, during which time the square box had been deleted as there was no evidence to support the use of other tetracyclines for this indication. The Secretariat was requested to commission a review to address this question. Expert comments were provided by Professor Tony Nunn.

The evidence identified in the review for efficacy of tetracyclines in children was mostly in children over eight years of age, and the majority of available evidence is for the use of doxycycline. No evidence was found for the use of other tetracyclines in the management of severe cholera.

The Subcommittee recognized that doxycycline and tetracycline have been recommended as the treatment of choice in Rickettsial infections. The review cited a Cochrane review of therapy for scrub typhus involving four trials, which demonstrated no difference between the use of doxycycline and tetracycline, or tetracycline and chloramphenicol in the management of scrub typhus.<sup>28</sup>

Minimal evidence was identified in the review for the efficacy of tetracyclines in the management of *Mycoplasma pneumoniae*, leptospirosis, or for the prophylaxis of *P.falciparum* and anthrax in children.

The Subcommittee acknowledged that children under eight years of age may develop permanent brown discoloration of their teeth, enamel defects and hypoplasia following the use of tetracyclines, which may be related to dose and duration of therapy. It was noted that a small amount of evidence exists that doxycycline may have less adverse effect on teeth than the other tetracyclines. In one study, only six out of 300 children and premature infants exposed to doxycycline developed discolouration of their teeth. A further small study not identified in the review, showed absence of tooth staining in 30 children aged between 2-8 years who received doxycycline treatment.<sup>29</sup>

The Subcommittee agreed that doxycycline is a useful antibiotic for the management of a wide range of infections as well as in the prophylaxis of infections of public health importance, and therefore removed the restricted indication for cholera. It was noted that evidence for efficacy and safety of other tetracyclines in children is limited, and therefore agreed upon that doxycycline be included on the List without a square box. An age restriction (over 8 years) should be applied when the tetracyclines are used to treat non-life-threatening infections.

### **Gentamicin (Review)**

The Subcommittee reviewed the inclusion of gentamicin on the List, as concerns had previously been raised regarding potential ethnic differences in ototoxicity associated with this drug. Expert reviews were provided by Drs Peter Kazembe and Anita Zaidi.

It was noted that most of the available evidence for safety of aminoglycosides in children is for gentamicin. The review identified a Cochrane systematic review of 11 studies (n=574 subjects)<sup>30</sup> that assessed safety and efficacy of once-daily dosing of gentamicin in neonates less than 28 days of life treated for sepsis. No ototoxicity or nephrotoxicity were seen in any patients, however limited numbers of preterm infants were included in these studies.

A second meta-analysis<sup>31</sup> of 24 randomized controlled trials compared once-daily dosing regimens with more frequent dosing in terms of patients with hearing loss

(assessed through both clinical and formal auditory testing). There were no cases of clinical hearing impairment, however on auditory testing, 2.3% of children treated with once daily administration of gentamicin were found to have auditory loss, compared with 2% of children treated with multi-dose administration of gentamicin (10/436 versus 8/406, relative risk 1.16; 95%CI 0.48 to 2.84). The majority of trials included in this meta-analysis were of small sample size, and although the two regimens seemed equivalent with respect to ototoxicity, only half of the studies actually incorporated formal audiometric testing. It was noted that less than 2% of children in either treatment group in this systematic review were found to have primary nephrotoxicity.

Another systematic review of 16 trials<sup>32</sup> comparing daily dosing with multi-dosing gentamicin in neonates aged less than 30 days on initiation of treatment demonstrated only one episode of ototoxicity in 210 neonates. No significant differences in toxicity between the two dosing regimens was seen.

The Subcommittee noted that there is limited evidence for the occurrence of ototoxicity in preterm infants following gentamicin use, although the majority of measurements for toxicity are carried out in the immediate post-treatment period only.

It was noted that toxicity correlates with gentamicin concentration in plasma and duration of use. The Subcommittee could find no documentation supporting an ethnic predilection for gentamicin toxicity in Chinese populations either within China or in other countries. The Subcommittee agreed that the majority of evidence demonstrates a low incidence of ototoxicity and nephrotoxicity following the use of gentamicin in children, but noted that there is a paucity of available evidence for occurrence of toxicity following aminoglycoside use in preterm infants, or on long-term follow-up. Systematic reviews failed to show a difference in incidence of gentamicin-associated ototoxicity with varying dosing regimens. On balance, given its broad potential for use in gram-negative infections, it was agreed that gentamicin should remain as the aminoglycoside on the List.

### **Sulfadiazine (Review)**

The Subcommittee considered the review of sulfadiazine for the treatment of toxoplasmosis in children. It had been noted in 2007 that it was not licensed to treat toxoplasmosis in children, and therefore a review of its use in children with particular regard to the treatment of toxoplasmosis was requested. Expert reviews were provided by Drs Stuart MacLeod and Tony Nunn.

Evidence cited in the Secretariat review to support the efficacy of sulfadiazine in the management of toxoplasma encephalitis included a Cochrane review<sup>33</sup> and several other randomized controlled trials involving adult HIV patients,<sup>34</sup> however there was limited evidence for its superiority over trimethoprim-sulfamethoxazole for this indication. Studies of the management of congenital toxoplasmosis included several longitudinal cohort studies,<sup>35, 36, 37</sup> which demonstrated sulfadiazine to be an efficacious and safe treatment for infected neonates. An improved outcome was seen in the majority of infected infants who were treated with combination sulfadiazine

therapy, however outcome was shown to be dependent on the length of treatment and the degree of disability at birth. The Subcommittee noted that there was no evidence to support the use of sulfadiazine in the treatment of *Nocardia* or in other infections.

Sulfadiazine treatment appeared to be well tolerated, with adverse reactions reported in approximately 5% of patients. No systematic reviews comparing oral versus intravenous sulfadiazine were identified, however it was noted that the majority of guidelines, including CDC and BNF 2006, recommend oral sulfadiazine in the management of toxoplasmosis. The majority of an oral dose is rapidly absorbed from the gastrointestinal tract and therefore no justification for an intravenous form could be made.

The Subcommittee agreed that there was sufficient evidence for the clinical efficacy and safety of oral sulfadiazine in children for the treatment of congenital toxoplasmosis. It was decided that intravenous sulfadiazine should be removed from the list and the oral tablet formulation should be deleted from section 6.2.2 of the List and moved to Section 6.5.4 (antitoxoplasmosis medicines). The need for an oral liquid formulation of sulfadiazine was also identified.

#### **6.2.4 Antituberculosis medicines (Review)**

At the July 2007 meeting, the Subcommittee noted that the FDCs listed for first-line treatment of TB in children needed to be reviewed to determine whether the currently recommended strengths were appropriate for children. The Secretariat commissioned a review of pharmacokinetic studies, and this was presented and considered at an informal meeting in July 2008. The report of the meeting is on the Subcommittee web site; the review of pharmacokinetic studies has not yet been published. A review of studies of ethambutol use in children was published in 2006.<sup>38</sup>

The recommendations for doses of pyrazinamide, isoniazid and rifampicin based on the assessment of the medical literature reviewed at the meeting are quoted below:

- 1. The panel recommends that the dose of PZ in children above 3 months of age should be 35 mg/kg (range 30-40) per day. The maximum daily dose should not exceed the recommended adult daily dose. If data are accessible, further analysis of the IPD from recent PK studies may increase the confidence in this recommendation.*
- 2. The panel recommends that the dose of isoniazid in children above 3 months of age for treatment or prophylaxis (treatment of latent TB infection) should be 10 mg/kg (range 10-15) per day. The maximum daily dose should not exceed the recommended adult daily dose.*
- 3. The panel recommends that the dose of RMP in children above 3 months of age should be 15 mg/kg (range 10-20) per day. Dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition. The maximum daily dose should not exceed the recommended adult daily dose. "*

The Subcommittee then considered what type of fixed-dose combination product would be needed to ensure sufficient flexibility to enable accurate administration of age-specific doses of each component medication. The three-drug formulation proposed in the July 2008 meeting (*isoniazid 100 mg/pyrazinamide 350 mg/rifampicin 200 mg*) was considered but not endorsed at the present time. The Subcommittee realizes that additional work is underway that when completed, should provide a more refined assessment as to what the composition and properties of an ideal formulation should be.

Currently, although the EMLc lists three fixed-dose combination products for children, no prequalified products exist in those strengths. The Subcommittee considered whether the FDCs currently on the List should be retained. Taking into consideration the public health importance of ensuring that treatment for TB is effective and noting that no products are currently prequalified, the Subcommittee recommended deletion of the existing FDCs on the grounds of potential underdosing, with associated risk of treatment failure, and lack of suitability, as multiple tablets of the existing strengths would be needed to ensure effective doses. The Subcommittee supported the urgent need for further research and reviews on this topic in order to define optimal doses, and recommended that the Expert Committee should consider progress on this at its meeting in March 2009.

#### **6.4.2 Antiretrovirals (New formulations)**

At its meeting in 2007, the Subcommittee considered that FDCs for children with HIV were clearly essential and endorsed 3 FDCs already on the adult list as appropriate for older children (listed in alphabetical order):

Lamivudine + nevirapine + stavudine: 150 + 200 + 30 mg.

Lamivudine + nevirapine + zidovudine: 150 + 200 + 300 mg.

Lamivudine + zidovudine: 150 + 300 mg.

In addition, the Subcommittee considered but rejected a number of applications for fixed-dose combination products for the treatment of children with HIV:

Lamivudine + nevirapine + stavudine, 40 + 70 + 10 mg, and 20 + 35 + 5 mg, Ranbaxy.

Lamivudine + nevirapine + zidovudine tablet, 30 + 60 + 60 mg, Ranbaxy.

Lamivudine + zidovudine, 150 + 300 mg scored tablet, GlaxoSmithKline.

Three new applications have been submitted to this meeting, for the following combinations:

1. Lamivudine + nevirapine + stavudine dispersible tablets 30+50+6 mg and 60 + 100 + 12 mg, Cipla.
2. Lamivudine + nevirapine + zidovudine tablet 30 + 50 + 60 mg, Matrix Laboratories.
3. Lamivudine + zidovudine tablet 30 + 60 mg, Matrix Laboratories.

Expert reviews' were provided by Mr Andy Gray and Dr Peter Kazembe; comments were received from the WHO Department of HIV.

The key problem for specifying FDCs is determining the appropriate doses of the components so that they are suitable for all children. For HIV, 'ideal doses' of components for first-line treatment have now been identified, by an expert group working with the WHO Department of HIV. These are published on the WHO web site. The most recent update of the 'ideal dosing table' is at: [http://www.who.int/hiv/paediatric/Sum\\_WHO\\_ARV\\_Ped\\_ARV\\_dosing.pdf](http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf).

The Subcommittee noted that the two applications from Matrix present no clinical evidence apart from bioequivalence studies. The applications are based on the recommended doses in the WHO guidelines, and the clinical evidence supporting these recommendations is summarized in an extensive report at: [http://www.who.int/hiv/paediatric/External\\_report\\_dosing\\_paediatric\\_ARVs.pdf](http://www.who.int/hiv/paediatric/External_report_dosing_paediatric_ARVs.pdf).

Both products are consistent with the 'ideal products' listed in the dosing table. Both have been registered in India and are under review by the WHO Prequalification Programme.

The application from Cipla is more complete, and as well as summary results of bioequivalence studies, includes a limited review of the relevant clinical literature. The doses of the components are consistent with the WHO 'ideal dose' recommendations for the lower-strength product; the higher-strength product is not listed in the WHO table. Both products have been prequalified by WHO. The main issue with this combination is the toxicity of stavudine, although this problem is well defined. The Subcommittee noted the comments from the WHO Department of HIV that zidovudine-containing combinations are generally preferred.

The Subcommittee recommended that as the proposed combinations containing zidovudine exist and comply with WHO 'ideal dose' requirements, they should be added to the EMLC. Quality of any individual product will have to be determined by regulatory review. The role of stavudine-containing combinations needs to be considered. While they may well be essential at present during the scale-up process of ARV treatment for children, their long-term usefulness is unclear. The Subcommittee therefore recommends that the combinations containing stavudine should be included on the EMLC, but reviewed again in the future. The Subcommittee also extensively discussed the roles of ritonavir-boosted lopinavir in paediatric HIV therapy and agreed that evolving safety data and consideration of how development influences the dose-plasma concentration-effect relationship for all medicines be considered in the determination of appropriate paediatric doses. In addition, the Subcommittee identified the need for heat-stable formulations of ritonavir-boosted protease inhibitors.

## 6.5 *Antiprotozoal medicines*

### 6.5.2 *Antileishmaniasis medicines*

#### **Liposomal amphotericin B (Inclusion)**

The Subcommittee considered the application submitted by the WHO Department of Control of Neglected Tropical Diseases (NTD) for listing liposomal amphotericin B in the EMLc, for the treatment of visceral leishmaniasis (VL). Expert reviews were prepared by Drs Shalini Sri Ranganathan (non-attending Temporary Adviser) and Anita Zaidi.

The Subcommittee noted that the incidence of this infection is increasing in different parts of the world and that children account for a good proportion of those with VL in disease-endemic areas. Morbidity and mortality related to this infection is substantial. Resistance to conventional therapy has been recorded, but there is inadequate information regarding the magnitude of this problem.

The available data, although not of good quality, suggest that liposomal amphotericin B is effective for the treatment of VL and is safe in children.<sup>39, 40</sup> However, the Subcommittee is concerned that there are insufficient data to understand how liposomal amphotericin B compares with the original formulation of this drug in terms of efficacy and safety in the treatment of VL. The Subcommittee noted that different dosages and schedules tested show good response and hence there could be flexibility in dosage schedule. Several regimens have used approximately 20 mg/kg total dose and WHO recommends this dosage.<sup>41</sup> The duration of in-patient therapy can vary, but is shorter than conventional therapies.

Safety data suggest that liposomal amphotericin B may be better than other therapies but there is a paucity of good quality data on which to base conclusions.

The cost of therapy with liposomal amphotericin B can be to be significantly higher than that of conventional therapies. The Subcommittee was made aware of the preferential pricing offer which could help in addressing the cost and availability issues associated with the procurement of liposomal amphotericin B in developing countries.

The Subcommittee has noted that liposomal amphotericin B is being used as first line therapy in some high-income countries. In other countries it is considered as second-line, mainly due to cost. The Subcommittee decided that liposomal amphotericin B should be added to the EMLc Core List for the treatment of VL. When the cost of the liposomal formulation is similar to that of the original formulation of amphotericin B, the liposomal formulation may be preferable given prior data in other fungal infections that support a lower incidence of nephrotoxicity. It also recommended that good quality clinical data on safety and efficacy of liposomal amphotericin B in children with VL be collected prospectively.

## Section 8. Antineoplastic, immunosuppressives and medicines used in palliative care

At its meeting in 2007, the Subcommittee noted that access to cytotoxic medicines for children was an important public health issue and that review of the cytotoxics listed, and the medicines for palliative care should be commissioned.

### 8.2 *Cytotoxic medicines (Review)*

The Subcommittee reviewed the documents provided to it. Expert comments were provided by Professor Noël Cranswick and Professor Dai Yao Hua. Additional comments were provided by Drs Ian Magrath, INCTR at Institut Pasteur, Brussels, Belgium, and Judith Margolin, Baylor College of Pharmacy, USA.

The documents included a brief overview of a sample of protocols used for ALL and a review of the uses of methotrexate. No detailed evidence was provided concerning the efficacy, relevancy or appropriate dosage of the medicines in children, the relative merit of one over the other, or an assessment of use within the developing world. Cytotoxic management of other common paediatric malignancies was also omitted from the review. However, it was noted that oral dexamethasone is an essential part of the majority of paediatric oncological protocols, including the United Kingdom, Children's Oncology Group 1882 (North America), Berlin-Frankfurt-Munster and Hong Kong SAR ALL protocol.

The review of methotrexate included a description of its use in the management of acute lymphoblastic leukaemia (ALL) and several studies were identified in which methotrexate was proven to be an effective therapy for ALL in children. Although intrathecal methotrexate forms part of standard care in the management of meningeal leukaemia and lymphomatous meningitis in children throughout the world, evidence for efficacy in children for this indication included in the application was limited. Its use in other indications was also evaluated and the Subcommittee noted that side-effects with methotrexate may be significant and multiple, and that the evidence that the benefits of methotrexate outweigh the harms when used as an immune modulator in the management of conditions such as juvenile rheumatoid arthritis, uveitis, inflammatory bowel disease, systemic lupus erythematosus (SLE), psoriasis and sarcoidosis was unclear.

The Subcommittee agreed that overall, the documents did not provide sufficient evidence to make an informed decision as to which cytotoxics should be included on the List. A more extensive review of the relative merits of these treatment approaches is required, particularly with regard to the developing country setting. The INCTR comments suggested potential modifications to the List that have already been done (e.g. deletion of levamisole and chlormethine) and potential additions without detailed assessment. They also note that certain cytotoxic medicines not included on the List e.g. ifosfamide, mesna, hydroxyurea are used in the management of paediatric cancers (e.g. chronic myeloid leukaemia, lymphomas and sarcomas), whereas other drugs on the List (e.g. fluorouracil) are rarely used in children.

An important question is the relevance of including cytotoxics on the WHO EMLc. On the one hand, countries that can afford to provide such care will develop protocols and formularies based on international standards, and presumably will have expertise available to administer the medicines appropriately. The relevance of the WHO List to these countries may be limited. On the other hand, deletion of all medicines and an indication that countries should make their own judgment is likely to be a significant barrier to access in some countries, as well as providing no guidance to countries wishing to start treatment programmes. The importance of treatment of HIV-related tumours in children, for example, is likely to increase and the availability of treatment is also likely to increase given donor priorities. In addition to the cost of treatment, most therapies are associated with significant side-effects requiring intensive support and monitoring, contributing to high individual patient costs. Diagnostic precision is also important.

The Subcommittee considered how best to advance the provision of evidence-based information on selection and use of these medicines so that it becomes a useful resource to countries, including, potentially, the development of appropriate treatment guidelines. This will require expanded consultation with experts and expert groups (e.g. Children's Oncology Group) to determine the most common paediatric malignancies, the medicines used to treat them and evidence (outcome-driven) suggesting their efficacy to improve both the quantity and quality of life.

It was therefore decided at this stage that the current list of cytotoxic medicines should remain unchanged.

#### **8.4 Medicines used in palliative care (Inclusion)**

The Subcommittee considered the review of medicines for palliative care commissioned by the Secretariat to ensure that appropriate medicines for the pharmacological management of the most prevalent and distressing symptoms in children with life-threatening and life-limiting conditions worldwide are included in the EMLc. Expert comments were provided by Drs Robert Peterson and Shalini Sri Ranganathan.

The Subcommittee noted that malignancy and HIV/AIDS were identified as the most common causes of childhood mortality appropriate to palliative care world wide and that 10 most frequent symptoms and symptom clusters (fatigue and weakness, pain, anorexia and weight loss, delirium and agitation, breathlessness, nausea and vomiting, constipation, depression, excess respiratory tract secretions and anxiety) were identified based on available data.

The Subcommittee noted that the evidence to support efficacy and safety of medicines used in the management of these symptoms was generally weak and therefore, several recommendations in the proposal were based on experience from clinical practice. It also noted that several medicines proposed for addition are not listed in the International Drug Price Indicator Guide and availability worldwide can be an issue.

For some of the medicines identified in the proposal but already included in other sections of the List, the Subcommittee was of the general opinion that the child friendly dosage forms recommended need to be included in the EMLc. These are oral dexamethasone, oral liquid ibuprofen (for bone pain), a rectal solution form of diazepam and variable dosage forms of morphine. The Subcommittee acknowledged that availability of these dosage forms may be a problem in some parts of the world but considered that inclusion on the EMLc was one important way to promote improved availability and access.

To ensure appropriate first- and second-line management of nausea and vomiting due to different pathophysiological mechanisms, the proposal suggested that antiemetics with different mechanisms of action are required. The review proposed the following medicines: cyclizine (tablet: 50 mg; injection: 50 mg/ml), an antihistaminic antimuscarinic antiemetic that is effective for vomiting centre-mediated nausea and vomiting and levomepromazine (tablet: 25 mg; injection: 25 mg/ml) for chemical trigger zone-mediated nausea and vomiting. Although there is lack of documented data on efficacy and safety, these two medicines are currently being used for this indication in some developed countries. Availability, especially of levomepromazine, may be a problem in many parts of the world. On balance, given that there is substantially more experience with the use of cyclizine, the Subcommittee recommended that it should be added to the EMLc in the dosage forms recommended specifically for use in palliative care.

The Subcommittee noted that the proposal recommends that laxatives are required for managing constipation, one of the most troublesome symptoms in palliative care. The options proposed were: (1) docusate sodium (capsule: 100 mg; oral liquid: 50 mg/5 ml) as a faecal softening agent for use in children (2) senna (oral liquid 7.5 mg/5 ml) as a stimulant laxative.

The Subcommittee agreed that docusate sodium to be better tolerated and cheaper than lactulose, which is often the only available alternative, and therefore recommended its inclusion. The Subcommittee also noted that current clinical practice supports the use of a stimulant laxative, senna, in the management of opioid-induced constipation and hence the oral syrup was included in the EMLc for use in palliative care.

For the management of respiratory tract secretions, the proposal suggested that hyoscine hydrobromide may provide some benefit in terminal care. Despite absence of data from large paediatric studies, the Subcommittee felt that the drug should be added to the EMLc. The Subcommittee particularly noted the potential usefulness of the patch presentation as an appropriate dosage form for use in children and decided, therefore to include the intravenous form and transdermal patch.

Midazolam is useful for managing anxiety and terminal agitation and delirium. The Subcommittee noted that there is insufficient evidence for superiority of one benzodiazepine over another. However, the use of intravenous midazolam as a short-acting benzodiazepine is valuable, and the Subcommittee also noted that the

intravenous form has been administered orally. It therefore recommended that midazolam should be included in the section on palliative care medicines for children.

Amitriptyline (10 mg tablet) is listed in the EML but was not endorsed for use in the treatment of depression in children at the meeting in 2007. The Subcommittee noted that this medicine is used in children for neuropathic pain and although there is, as for most other palliative care medicines in children, a lack of formal studies, it appears to be safe and effective. Hence the Subcommittee recommended that this medicine should be added to the EMLc specifically for use in palliative care.

The Subcommittee considered the general principle of whether medicines listed for palliative care should also have indications of age restrictions. On the one hand, it was noted that several of the medicines added to the List in this Section did not have evidence of efficacy and safety throughout all ages. Specifically:

- cyclizine is not licensed for use in children under 6 years;
- docusate sodium is not licensed for use in children under 6 months;
- senna is not licensed for use in children under 2 years.

The Subcommittee considered that the licensed indications may not always reflect existing evidence, and also noted the importance of access to these products for children in palliative care, and therefore decided not to indicate age restrictions on the use of these products for this purpose.

## Section 12. Cardiovascular medicines

### Quinidine (Review)

#### *Complementary list*

The Subcommittee considered the review of quinidine that proposed its deletion from the EMLc. At its 2007 meeting, the Subcommittee identified antiarrhythmics as a class of medicines for which further information was required before any could be endorsed as essential in children. Expert comments were provided by Dr Helena L. Coelho and Professor Noël Cranswick.

The Subcommittee noted that there is paucity of data on need for, and use of, antiarrhythmics in children generally, but acknowledged that the effects of quinidine are likely to be similar to those observed in adults. In adults, there is good evidence to show that quinidine suppresses atrial fibrillation.<sup>42</sup> However, there is also high quality evidence to show that use of this medicine is associated with higher rates of potentially fatal adverse events like Torsade de Pointes<sup>43</sup> and that mortality is higher with use of this medicine as compared to controls. Adverse events can even occur at therapeutic and sub-therapeutic serum levels and occasionally without marked QT prolongation. There is also the possibility of dangerous drug interactions with commonly used medicines.

Regulatory authorities have not approved this medicine for paediatric use. In the absence of evidence to establish public health need and efficacy and safety, the Subcommittee recommended that quinidine not be included in EMLc.

### **Rheumatic fever and rheumatic heart disease (Review)**

The Subcommittee considered the review on antibiotics for the prevention and treatment of rheumatic fever (RF) and rheumatic heart disease (RHD) in children, commissioned to determine whether the antibiotics listed currently are appropriate and adequate.

The Subcommittee noted that the burden due to RF and RHD is high, especially among children in less developed countries. Antibiotics are proven to be effective in primary prevention, treatment of acute rheumatic fever and for secondary prophylaxis.

For all three situations, benzathine benzyl penicillin is recommended as the first-line therapy.<sup>44</sup> Evidence shows that this antibiotic can reduce recurrences and that IM therapy is better than oral therapy for this outcome.<sup>45</sup> However, oral phenoxymethyl penicillin is an alternative if injections are unacceptable or not possible. In patients with hypersensitivity to penicillins, erythromycin is the recommended antibiotic. These three antibiotics are listed in the current EMLc.

The Subcommittee recommends that the antibiotics listed currently in the EMLc (as shown below) are adequate for the prevention and treatment of RF and RHD:

- Benzathine benzyl penicillin:  
Powder for injection: 900 mg (=1.2 million IU) in 5-ml vial; 1.44 g (=2.4 million IU) in 5-ml vial.
- Phenoxymethyl penicillin:  
Powder for oral liquid: 250 mg (as potassium salt) in 5 ml;  
Tablet: 250 mg (as potassium salt).
- Erythromycin:  
Capsule or tablet: 250 mg (as stearate or ethyl succinate);  
Powder for oral liquid: 125 mg (as stearate or ethyl succinate).

## **Section 13. Dermatological medicines (topical)**

### **Dermatological medicines (Review)**

The Subcommittee considered the review on dermatological medicines prepared by the International League of Dermatological Societies (ILDS). Expert comments were provided by Dr Shalini Sri Ranganathan and Professor Harshi Sachdev. Additional comments were provided by MSF.

Diseases of the skin are common in children and are among the leading reasons for visits to primary health care services.<sup>46</sup> Several different topical and systemic medicines are required to treat the varied conditions affecting the skin. The Subcommittee noted that the review identified 10 diseases as priority and that recommendations for addition and deletion were made in addition to retaining most medicines in the list.

The Subcommittee noted that the review by the International League of Dermatological Societies recommends that the following medicines are retained:

- Miconazole and Whitfield's ointment (benzoic acid + salicylic acid) (Section 13.1).
- Silver sulfadiazine 1% cream, gentian violet 0.5% in alcohol or water and potassium permanganate 1/10,000 aqueous solution (Section 13.2).
- 1% hydrocortisone cream and 0.1% betamethasone cream and calamine lotion (Section 13.3).
- Salicylic acid preparations, benzoyl peroxide 5% cream or lotion and urea 5% or 10% cream or ointment (Section 13.5).
- 10-25% benzyl benzoate, permethrin cream/solution (Section 13.6).

Povidone iodine 10% solution and chlorhexidine solution listed in section 15.1, are also useful for topical treatment of skin diseases.

Cloxacillin, amoxicillin, erythromycin, doxycycline, benzyl penicillin, griseofulvin, aciclovir, chlorphenamine, cefalexin and ivermectin are also required for managing skin diseases resulting from infectious causes and are listed in other sections of the EMLc.

The Subcommittee noted that the review has recommended the addition of the following medicines – econazole cream (13.1); tetracycline 3% ointment (13.2); lindane cream/lotion (13.6); crotamiton ointment (13.6); petrolatum and oral terbinafine.

As miconazole ointment or cream is listed in the EMLc with a square box addition of econazole is not required.

Although topical tetracycline may be useful for certain skin conditions, there is insufficient clinical data on its efficacy and safety in children to determine whether it is to be listed. The Subcommittee noted the recommendation that neomycin sulfate + bacitracin ointment (13.2) be deleted from the List. Information from the review suggested that neomycin + bacitracin is associated with allergic manifestations and better topical applications are currently available. The Subcommittee concluded that insufficient information is currently available and proposed a review of the comparative effectiveness and safety of common antibiotics for the treatment of skin infections in neonates, particularly pyoderma and omphalitis.

The Subcommittee noted that resistance to first-line scabicides and pediculocides has appeared and so there is a need for alternate therapy. However, it was concerned

about the safety profile of lindane and in the absence of a more detailed assessment of the safety, decided not to include it on the EMLc at this time. While crotamiton appears to be safe in children, data to support its effectiveness in comparison with permethrin were not provided and would need to be considered before it could be added to the EMLc.

The Subcommittee felt that there was insufficient evidence to determine that petrolatum met the criteria of an essential medicine and hence it was not included on the EMLc.

There is evidence that oral terbinafine is useful in treating *tinea capitis*, commonly seen in children. The Subcommittee reconsidered the prior review of oral antifungals in children (2007) and concluded that there was insufficient basis for including oral terbinafine on the EMLc at the present time.

The Subcommittee noted the recommendation that dithranol preparation (13.5) be deleted from the List given its caustic potential. This recommendation was accepted.

## Section 15. Disinfectants and antiseptics

### Chlorhexidine (New formulation)

The Subcommittee considered the application to include 4% chlorhexidine in the EMLc for topical cord care in settings where risk of umbilical cord infections is high. Expert comments were provided by Drs Jacqueline Deen and Gregory Kearns.

The Subcommittee noted that the risk of umbilical cord infections is higher in areas where neonatal mortality rates are already very high and that these infections contribute significantly to neonatal mortality. Cord infection rates are higher in areas where home delivery rates are high, where clean delivery is not universally guaranteed and where traditional practices of cord care increase the risk of infection. There is a general consensus that in unclean deliveries, topical antiseptics for cord care may be of use in preventing infections.

Systematic reviews do not show superiority of any one antiseptic. However, a recent large community-based cluster randomized trial in Nepal,<sup>47</sup> showed that chlorhexidine 4% reduces incidence of omphalitis as compared to dry care. A reduction in neonatal mortality was also observed, when treatment was started within 24 hours of birth. Another recent trial done in Italy<sup>48</sup> failed to confirm these findings. One explanation for the discrepancy in the trial results is the different standards of perinatal care in the two countries.

Chlorhexidine is currently listed in the EMLc, with a square box, as solution 5% (digluconate) for dilution, in the section 15.1 (antiseptics). The Subcommittee noted that for the RCT which showed benefit, the chlorhexidine 4% was prepared for use by diluting a 20% commercially available solution.<sup>47</sup> The options are therefore to add a 20% solution of chlorhexidine digluconate and specify it for dilution or add 7.1% as proposed in the application. In the absence of a commercially available 7.1% solution,

the Subcommittee decided to include a 20% solution as digluconate on the List, specifying the dilution required in the proposed WHO Model Formulary for Children.

## Section 17. Gastrointestinal medicines

### Pancreatic enzymes (Inclusion)

The Subcommittee reviewed the application for the inclusion of pancreatic enzymes on the List, for the management of severe pancreatic insufficiency. Expert comments were provided by Professor Harshi Sachdev and Dr Elizabeta Zisovska.

The Subcommittee noted that the majority of paediatric patients with pancreatic insufficiency suffer from cystic fibrosis, although several other conditions (e.g. chronic pancreatitis and post-gastric surgery) may also contribute to this condition. It was acknowledged that cystic fibrosis occurs on a global basis, and that pancreatic insufficiency may be present in up to 90% of these patients. The resulting malnutrition may lead to a multitude of negative clinical outcomes, including lower life expectancy, poor growth, increased susceptibility to infections, and deterioration in lung function.

The Subcommittee noted that the application cited several good quality randomized trials, which appeared to support the use of pancreatic enzymes for treatment of pancreatic insufficiency in cystic fibrosis. A significant difference in mean protein and fat absorption was seen when comparing placebo to pancreatic enzyme replacement therapy, however the aim of the majority of studies was to evaluate different doses and formulations. Two randomized controlled studies<sup>49,50</sup> carried out by the manufacturer of Creon, Solvay, were described, where a CFA (co-efficient of fat absorption) of up to 89.1% following Creon treatment was observed. Similar efficacy was demonstrated between different preparations included in the application.

Limited studies involving the use of pancreatic enzyme therapy in the management of conditions other than cystic fibrosis were included in the application, and the Subcommittee noted that evidence for safety and efficacy in infants less than six months was limited.

It was the conclusion of the Subcommittee that sufficient evidence exists for the efficacy and safety of pancreatic enzyme replacement therapy in children, with resulting improvement in morbidity and mortality of patients with severe pancreatic insufficiency. Given the need for the dose to be monitored and titrated according to clinical response, it was agreed that pancreatic enzymes should be included on the Complementary List.

Further discussion by the Subcommittee focused on the recent warnings about phthalates in the formulations and their potential safety implications.

## 17.2 Antiemetic medicines (Review)

At its 2007 meeting, the Subcommittee requested a review of the choice of antiemetics for inclusion on the EMLc. The Secretariat commissioned a review, considered below. It was noted that antiemetic medications are not currently included in any of the major guidelines (American Academy of Pediatrics, CDC, WHO) for use in children with acute gastroenteritis. Expert comments were provided by Professor Prakash Mohan Jeena.

The commissioned review included a number of systematic reviews evaluating the effectiveness of antiemetics in the management of acute gastroenteritis in children. It was noted that although the studies demonstrated ondansetron to be significantly superior to placebo in preventing vomiting, none of the studies supported the routine use of antiemetic medications in the management of acute gastroenteritis in children. The Subcommittee also noted that the majority of studies reported a significant increase in side-effects associated with the use of antiemetics.

Overall there was insufficient evidence to support the routine use of antiemetic medications in the management of children with gastroenteritis, and potentially a high risk of associated adverse events, negating any significant benefit in children. However, the Subcommittee noted that antiemetic medicines were important in the context of post-operative nausea and vomiting as well as in conjunction with chemotherapy. It therefore recommended that before deleting the existing medicines a further assessment of this class of drugs in post-operative patients and those receiving cancer chemotherapy, should be carried out, especially with regard to newer products, such as 5-HT<sub>3</sub> antagonists.

## Section 18. Hormones, other endocrine medicines and contraceptives

### Hydrocortisone and fludrocortisone (Inclusion)

The Subcommittee considered the application for the inclusion of the adrenal hormones fludrocortisone and hydrocortisone to the List. Expert comments were provided by Dr Stuart Macleod and Professor Tony Nunn. Numerous external comments in support of the proposal were received from health professionals, associations and individuals.

The Subcommittee noted that hydrocortisone and fludrocortisone are used in the management of primary and secondary aldosterone deficiency caused by congenital adrenal hyperplasia (CAH) and Addisons disease, that both medications are licensed for use in all ages, and that treatment should be of life-long duration. It was noted that fludrocortisone is currently the only mineralocorticoid available for aldosterone replacement in CAH, and that consequently there are no comparative efficacy or safety studies for the management of mineralocorticoid deficiency in CAH.

The application identified a retrospective study of 484 patients from five European countries, which demonstrated a decrease in mortality rate from 11.9% in untreated patients to 4.3% in those patients who were treated with fludrocortisone.<sup>51</sup>

Only one small study<sup>52</sup> of nine patients comparing hydrocortisone with prednisone for the management of CAH was included in the application, which showed that prednisolone had significantly greater adverse effects on growth than hydrocortisone. It was acknowledged however that other glucocorticoids such as dexamethasone and prednisolone are generally avoided in children due to adverse effects on growth.

The Subcommittee agreed that fludrocortisone and hydrocortisone are both essential medicines for children in the management of congenital adrenal hyperplasia and adrenal insufficiency, and included them on the EMLc.

## **Section 24. Psychotherapeutic medicines (Review)**

At its meeting in July 2007, the Subcommittee requested a review of the section on psychotherapeutic medicines to determine what was essential in addition to the products considered at that meeting. In particular the sections on anxiety and sleep disorders, obsessive-compulsive disorders and panic attacks, and substance abuse were highlighted as needing further review. The Secretariat commissioned a review, published for discussion at the meeting. Expert comments were provided by Dr Kalle Hoppu and the WHO Department of Mental Health and Substance Abuse.

The Subcommittee decided that the review is best considered as a preliminary overview; as has been pointed out by the Department of Mental Health and Substance Abuse, there needs to be more detailed summaries of evidence prepared before the additions of medicines to the EMLc as suggested could be supported. It is difficult to support addition of any new medicines on the basis of the information currently presented.

The Subcommittee recommended that a review be undertaken by the Secretariat to identify the most common mental health disorders in children that require medication and that this information should be used as the basis for further development of this section of the EMLc. The Subcommittee recommended retaining chlorpromazine and haloperidol at present but recognized that their patterns of use support inclusion on the Complementary List. There was no change for the listing of fluoxetine at this time.

## **Section 25. Medicines acting on the respiratory tract**

### **Salbutamol (Review)**

Oral salbutamol is currently included on the list in liquid and tablet formulation. In July 2007 the Subcommittee noted that these formulations are rarely used in the management of childhood asthma in many countries and requested a review of the evidence for the use of these forms, with particular emphasis on young children with viral-related wheeze. A review was subsequently received by the Secretariat. Expert comments were provided by Professor Noël Cranswick and Mr Andy Gray.

Given the superiority of inhaled salbutamol over oral salbutamol for the management of asthma, the lack of evidence for the use of bronchodilators in bronchiolitis, and the paucity of evidence for the use of oral salbutamol in children with viral wheeze, the Subcommittee agreed that at present, oral salbutamol should only be considered for use when treatment with inhaled asthma medications is not feasible. The EMLc was annotated to reflect this recommendation.

### Surfactant (Inclusion)

The Subcommittee reviewed the application for the inclusion of surfactant on the List for the prophylaxis and management of primary respiratory distress syndrome in pre-term infants, and secondary surfactant deficiency in infants. Expert comments were provided by Professor Noël Cranswick and Dr Elizabeta Zisovska.

High quality evidence demonstrating that both prophylactic and rescue surfactant improve clinical outcome in premature neonates was identified in the application. This included a Cochrane systematic review<sup>53</sup> of seven randomized controlled trials in which clinical outcomes were assessed following prophylactic administration of synthetic surfactant to premature infants aged between 25 to 34 weeks gestation, and birth weights between 500 to 1350 grams. The meta-analysis showed a statistically significant decrease in the risk of pneumothorax, a decrease in the risk of pulmonary interstitial emphysema, and a decrease in risk of neonatal mortality. However an increased risk of developing patent *ductus arteriosus* and pulmonary haemorrhage was demonstrated.

The Subcommittee noted that the European Consensus Guidelines recommend the use of natural over synthetic surfactant as a prophylactic approach in infants less than 27 weeks gestation, and to those between 26-30 weeks gestation if intubation is required in the delivery room or if no prenatal corticosteroids have been received. The American Academy of Paediatrics guidelines suggest that surfactant should be given to infants with RDS as soon as possible after intubation, regardless of gestational age or exposure to prenatal corticosteroids.

A systematic review<sup>54</sup> which included 11 trials showed that although the use of natural versus synthetic surfactant resulted in a significant reduction in the risk of pneumothorax and mortality, there was a trend towards an increase in overall intraventricular haemorrhage in the natural surfactant group.

The Subcommittee noted that limited evidence is available for the optimal method of surfactant administration and that high quality evidence is lacking for the use of surfactant in other conditions such as persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, neonatal pulmonary haemorrhage and meconium aspiration syndrome.

Despite evidence for an increased risk of patent *ductus arteriosus*, pulmonary haemorrhage and intraventricular haemorrhage following treatment with surfactant therapy, the benefits of use in management of respiratory distress syndrome in the

neonatal population clearly outweigh the risk. Costs of surfactant were noted to be high. The Subcommittee concluded that the application had identified high quality evidence for the use of surfactant in the management of respiratory distress syndrome in premature infants. It was added to the EMLc and placed in a new section devoted to neonatal medicines and categorized as a Complementary medicine given the nature of its use.

## Section 27. Vitamins and minerals

### Retinol

The WHO Department of Child and Adolescent Health and Development has commissioned a review of the evidence of potential benefit of prophylactic/routine administration of Vitamin A to neonates and infants under six months, with a view to updating the current recommendations about its use. The proposal to delete the 50 000 IU formulation currently on the List arose from the results of the review. Expert comments were provided by Drs Macleod and Petersen.

The two reports, provided as confidential drafts to the Subcommittee, were the manuscript version of the systematic review of neonatal Vitamin A supplementation<sup>55</sup> and the report to WHO on the benefits and safety of Vitamin A supplementation in the first six months of infant life.<sup>56</sup> Both are comprehensive systematic reviews and both found that the existing evidence shows no mortality or morbidity benefit of routine supplementation in these age groups. The Subcommittee noted that administration of this drug to young infants has been associated with an increased occurrence of bulging fontanelle.

An additional five Cochrane reviews were identified<sup>57, 58, 59, 60, 61</sup> examining administration of Vitamin A to other subgroups of children: low birth weight infants, children with cystic fibrosis, children with measles, for prevention of lower respiratory tract infections, and non-measles pneumonia in children under seven years of age.

In low birth weight children, most studies reported use of intramuscular Vitamin A. There was a trend towards benefit in terms of survival and reduced oxygen requirement, but most of the outcomes analysed were not statistically significant. No studies were identified in the review of cystic fibrosis. In the review of measles treatment, Vitamin A was administered as 100 000 or 200 000 IU and was found to reduce mortality. The reviews of non-measles pneumonia and lower respiratory tract infections found evidence showing no benefit of Vitamin A in children under seven years of age.

The Subcommittee considered that there was no clear need for a 50 000 IU oral dose for routine prophylaxis of vitamin A deficiency during the first six months of life. The 50 000 IU dosage form is also not appropriate for routine supplementation in children over six months in whom the recommended dose is 100 000 or 200 000 IU. Therefore the only potential use for the low-dose capsule would be for the outpatient treatment

of clinically proven Vitamin A deficiency in the neonate and infants under six months of age; a condition that is exceedingly rare. The Subcommittee recommended that the 50 000 IU dosage form be deleted from the List.

## **NEW Section 28. Ear, nose and throat conditions in children**

The Subcommittee considered the review which was commissioned to identify essential medicines for the treatment of ear, nose and throat conditions in children. Expert comments were provided by Dr Kalle Hoppu and Professor Prakash Mohan Jeena.

Based primarily on South African guidelines and WHO guidelines for treating ENT conditions in children, the priority conditions identified were acute croup, epiglottitis, epistaxis, otitis externa, otitis media (acute and chronic), rhinosinusitis and sore throat. The Subcommittee noted that many medicines required for treating these conditions are already listed. However, several more need to be considered for addition. These include preparations for both topical and systemic use. There is a lack of documented evidence for efficacy and safety for most medicines that need to be considered for addition. Most available data are from studies in adults or from those involving both adults and children. However, these medicines are recommended in widely accepted guidelines.

The Subcommittee noted that there is evidence to show that antibiotic ear drops are of benefit in the treatment of otitis externa. There is evidence to suggest that quinolone ear drops are superior to other otic antimicrobial formulations. The Subcommittee considered the importance of available information regarding combination antimicrobial agent – corticosteroid formulations for the treatment of otitis externa<sup>62</sup> and found no compelling evidence to support the inclusion of combination products.

The Subcommittee therefore recommended that acetic acid ear drops and ciprofloxacin ear drops be added to the EMLc, the latter with a square box annotation.

The Subcommittee decided that based on available evidence, the inclusion of a nasal corticosteroid could be recommended. Further, the Subcommittee recommended the inclusion of a decongestant nasal spray/nose drops, listing xylometazoline with a square box annotation. Topical ephedrine was not included in recognition of its abuse potential.

The Subcommittee requested a full proposal for a non-sedating antihistamine.

## **NEW Section 29. Essential medicines for neonates**

The Subcommittee reviewed the application for inclusion of a separate section for neonates. In October 2007, the Expert Committee recommended that (1) the Subcommittee should consider whether it would be appropriate to develop a separate section of the List for neonates (2) if a separate section is recommended, should it be retained for the 'master list' and (3) how to prioritize work in this neglected area.

The Secretariat prepared the review provided to the Subcommittee. Expert comments were provided by Professor Noël Cranswick and Dr Gregory Kearns. General issues noted were:

- The paucity of high quality evidence for the use of medications in the neonatal period and the subsequent off-label and unlicensed use in this population are major problems.
- A more detailed and systematic review of available evidence for efficacy and safety of the medicines recommended for neonates may be required.
- Medicines were categorized as *recommended* essential medicines for neonates, *missing* essential medicines for neonates, medicines *requiring further review* before a recommendation for use in neonates can be made, and medicines *not* recommended for neonates.

The Subcommittee noted that medicines currently missing from the List, and recommended exclusively for use in neonates were:

1. Intravenous ibuprofen or indomethacin – injectable non-steroidal anti-inflammatory medicines for use in the management of patent ductus arteriosus (PDA) in preterm infants. It was noted that there is evidence that ibuprofen and indomethacin are equivalent in efficacy for this indication.<sup>63</sup> This meta-analysis, not included in the application, of 11 trials comparing the treatment therapies for management of PDA in the preterm infant, showed that ibuprofen was as effective as indomethacin in closing the PDA. No significant differences were found in the incidence of complications, except for less renal impairment with ibuprofen.
2. Prostaglandin E1 or E2 injection – used to maintain patency of the *ductus arteriosus* when a cyanotic lesion or interrupted aortic arch presents in a newborn. No systematic reviews were identified for the efficacy of prostaglandin in the management of patent *ductus arteriosus*, but this therapy is recommended in most clinical treatment guidelines.
3. Surfactant – See Section 25 – Medicines Acting on the Respiratory Tract.

Given that the Secretariat review identified only four medicines that are for exclusive use within the neonatal population, the Subcommittee recommended inclusion of a new section for these specific medicines for neonatal care. These were:

- caffeine citrate, already included under section 25.
- the inclusion of ibuprofen injection in this new section of the List, with a square box to indicate that indomethacin may be an appropriate alternative.
- the inclusion of Prostaglandin E1 or E2 injection
- surfactant (see Section 25).

Given that caffeine citrate is recommended for use in health facilities generally and does not require an intensive care unit, it was considered that it should remain on the Core List. The other medicines were included on the Complementary List.

The Subcommittee then considered addition aspects of the use of other medicines, already on the EMLc, in neonates. Comments were received from the WHO Child and Adolescent Health and Development Department, which questioned the need to include chloramphenicol, vitamin A, zinc sulfate and aciclovir 3% for neonates.

There is no evidence for efficacy of oral zinc in children under six months of age. A recent review from the Cochrane Collaboration identified 18 randomized controlled trials that compared zinc with placebo in young children. This included two large trials that were conducted in children aged less than six months with acute diarrhoea, and showed no evidence of an effect on any of the outcomes.<sup>64</sup>

Evidence for the efficacy of chloramphenicol specifically in the neonatal population is limited. A Cochrane review showed equivalent efficacy of ceftriaxone or cefotaxime with conventional antibiotics (including chloramphenicol) when given for the management of acute bacterial meningitis.<sup>65</sup>

Neonates with suspected HSV infection, including those with skin, eye or mouth disease, should be treated with intravenous aciclovir. There is no evidence for the efficacy of topical aciclovir in the management of neonatal herpes infections.

On the basis of the review, medicines on the EMLc used in neonatal care were identified and are included in Annex 6 to this report. The Subcommittee considered that a separate neonates list could cause unnecessary confusion and that an annex listing medicines that can be safely used in neonates was the best option at the present time.

## 5. Summary of recommendations

### Section 4: Antidotes and other substances used in poisonings

#### 4.2 *Specific*

- NAC oral solution added.

### Section 6: Anti-infective medicines

#### 6.2.1 *Beta Lactam medicines*

- **Cefalexin** – capsule, tablet and powder for dilution added.
- **Cefotaxime** – added to Complementary List for use in hospitalized neonates.
- **Ceftazidime** – request for review removed.
- **Ceftriaxone** – age restriction added to above 41 weeks corrected gestational age; note added regarding avoidance of use in administration with calcium and in infants with hyperbilirubinemia; request for review removed.
- **Imipenem-cilastin** – note added that meropenem is indicated for the treatment of meningitis in children over the age of 3 months; request for review removed.
- **Procaine benzylpenicillin** – age restriction removed; note added that it is not recommended as first-line treatment for sepsis and/or meningitis; request for review removed.

#### 6.2.2 *Other antibacterials*

- **Azithromycin** – age restriction removed.

- **Ciprofloxacin** – removal of note for use only in *Shigella* infections; IV and oral liquid formulation added; request for review removed.
- **Doxycycline** – age restriction added for use in children under 8 years of age in non-life threatening conditions; removal of note regarding use only in cholera; request for review removed; 50 mg tablet and oral liquid added.
- **Erythromycin** – IV formulation deleted; request for review removed.
- **Gentamicin** – request for review removed.
- **Sulfadiazine** – intravenous form deleted; oral form moved from Section 6.2.2 to Section 6.5.4.

#### **6.2.4 Antituberculosis medicines**

- Deletion of fixed-dose combination antituberculosis medications (rifampicin + isoniazid, rifampicin + isoniazid + pyrazinamide).

#### **6.4.2.3 Protease inhibitors**

- Addition of new doses of fixed-dose combination tablets for antiretroviral medicines.

#### **6.5.2 Antileishmaniasis medicines**

- Liposomal amphotericin B added to the Core List antileishmaniasis medicines.

### **Section 8: Antineoplastic, immunosuppressives and medicines used in palliative care**

#### **8.4 Medicines used in palliative care**

- Ten new medicines added (amitriptyline, cyclizine, dexamethasone, diazepam, docusate sodium, hyoscine hydrobromide, ibuprofen, midazolam, morphine and senna).

### **Section 10: Medicines affecting the blood**

#### **10.2 Medicines affecting coagulation**

- Heparin sodium strength 20 000 IU deleted.

### **Section 12: Cardiovascular medicines**

#### **12.5 Antithrombotic medicines**

- Antithrombotic medicines section deleted.

### **Section 13: Dermatological medicines (topical)**

#### **13.5 Medicines affecting skin differentiation and proliferation**

- Dithranol preparation deleted.

## **Section 15: Disinfectants and antiseptics**

### **15.1 Antiseptics**

- 20% chlorhexidine digluconate solution added.

## **Section 16: Diuretics**

- Spironolactone – strength changed to 5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml (previously 1-20 mg/ml).

## **Section 17: Gastrointestinal medicines**

- Pancreatic enzymes added to the Complementary List.

## **Section 18: Hormones, other endocrine medicines and contraceptives**

### **18.1 Adrenal hormones and synthetic substitutes**

- Fludrocortisone and hydrocortisone added to the List.

### **18.5 Insulins and other antidiabetic agents**

- Insulin injection strength 40 IU/ml deleted.

## **Section 24: Psychotherapeutic medicines**

### **24.1 Medicines used in psychotic disorders**

- Chlorpromazine and haloperidol moved to the Complementary List.

## **Section 25: Medicines acting on the respiratory tract**

### **25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease**

- Oral salbutamol – note added that treatment should only be considered when inhaled asthma therapy is not feasible.

## **Section 26: Solutions correcting water, electrolyte and acid-base disturbances**

### **26.2 Parenteral**

- Glucose (4%) with sodium chloride (0.18%) deleted.
- Potassium chloride strength 7.5% and 15% added, 11.2% deleted.

## **Section 27: Vitamins and minerals**

- Retinol – 50 000 IU dosage form of Vitamin A deleted from the List.

### **Section 28: Ear, nose and throat conditions in children**

- New ENT section created.
- Acetic acid drops, budesonide, ciprofloxacin drops and xylometazoline spray added to the List.

### **Section 29: Essential medicines for neonates**

- New section created for specific medicines in neonatal care.
- Caffeine citrate moved to this section from Section 25.2.
- Surfactant, prostaglandins and intravenous ibuprofen added.
- Medicines used in neonatal care identified and included in Annex 6.

### **Table 1. Age restriction table**

- New additions – ceftriaxone, xylometazoline.
- New deletions – azithromycin, clindamycin, procaine benzylpenicillin.

DRAFT

**Summary of NEW reviews/applications requested during the Subcommittee meeting:**

- Appropriate medicines for use in resuscitation in children.
- Essential medicines for management of neuropathic pain in children, including the role of lamotrigine, amitriptyline and gabapentin.
- Review of liposomal amphotericin B as treatment of fungal infections in children.
- Antimonials as essential medicines for leishmaniasis, and whether they should be on the Core or Complementary List.
- Safety and efficacy of streptomycin in childhood TB.
- Review of safety of topical antibiotics, including tetracycline ointment in neonates.
- Clinical use of ondansetron in children.
- The role of leukotriene antagonists in the management of childhood allergic rhinitis.
- Application for heat-stable protease inhibitors for HIV management.
- Comparison of sulfadiazine and co-trimoxazole in the treatment of toxoplasmosis.
- Application for glucagon.
- Development of child-friendly equipment for medicine administration for all ages.
- Review use of methylene blue in children.
- Review use of oral iron/lead chelators in children.
- Assessment of two new clinical trials on safety and efficacy of procaine benzylpenicillin in neonates.

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## Annex 1: Declaration of interests of Subcommittee Members

### The Members of the Subcommittee reported the following:

Professor Noël Cranswick reported being an investigator on trials for GlaxoSmithKline, Quintiles, Novartis, Uriach, Biomarin and Biota but not for any products or related products to those being considered at the meeting, and also holding shares in Biota through a family trust.

Mr Andy Gray reported having accepted travel support and honoraria from AstraZeneca, Aspen Pharmacare for continuing professional development lectures and being a study pharmacist for the International Clinical Trials Unit and Center for the AIDS Programme of Research in South Africa in KwaZulu-Natal. He also reported being a director of a government funding agency for biotechnology, and being a member of the Scheduling and Naming Committee of the Medicines Control Council of South Africa.

Dr Kalle Hoppu reported receiving lecture fees from Norit Pharmaceuticals Netherlands, Leiras Ltd. Finland (2005) and Oy Swedish Orphan Ab Finland (2008). Dr Hoppu reported providing consultation advice once to Lundbeck A/S Denmark provided through the Clinical Research Institute Helsinki University Central Hospital Ltd/Finnish Investigators Network for Paediatric Medicines.

Dr Gregory Kearns reported providing consultancy services for Abbott, Biodelivery Sciences, Santarus, Mead Johnson, Wyeth Pharmaceuticals, Cubist Pharmaceuticals, Schwarz Pharma, Proctor and Gamble, Orexigen, Tyco Healthcare, Altana Pharma and Centcor. In addition, Dr Kearns reported that his employer holds research contracts related to child health with the private sector. He also serves as a member of the U. S. Food and Drug Administration Clinical Pharmacology Advisory Committee, and provides consultation to the National Institutes of Health regarding paediatric drug development.

Professor Prakash Mohan Jeena declared being a principal investigator on a trial of protease inhibitors in HIV (GSK) and receiving travel support and honoraria for lectures from GlaxoSmithKline, Wyeth and Sanofi-Pasteur. He also chaired the essential drugs program for children in South Africa.

Dr Anita Zaidi reported that her department received research funding from Wyeth Pharmaceuticals and GlaxoSmithKline for work on vaccines.

Dr Peter Kazembe reported that his employing institution received some funding from The Abbot Fund, through Baylor College of Medicine, USA.

Mrs Jehan Mohammed Ali Al-Fannah and Dr H.L. Coelho and reported no conflict of interest.

**The Temporary Advisers reported the following:**

Dr Stuart Macleod reported serving as Executive Director of the Child and Family Research Institute, Vancouver, and as Associate Dean (Research) University of British Columbia. Both institutions hold child health research contracts with the private sector, but he is not principal investigator on any of these contracts. He has also provided consultation and has served on advisory committees for federal and provincial governments in Canada.

Dr Robert Peterson reported receiving travel expenses to attend the Board meetings of the Institute for Regulatory Science, Centre for Medicines Research International, and also for being a member of the Expert Drug Advisory Committee of the Canadian Agency for Drug and Health Technology Assessment.

Professor H. P. S. Sachdev reported receiving honoraria for speaking at the National Probiotic Symposium (India, 2007) and the National Indian Academy of Paediatrics Conference (2007) on the use of probiotics and zinc to treat diarrhoea. He also served on policy committees established by the Government of India.

Professor Anthony Nunn provided advice to the European Medicines Agency and the UK Government Commission on Human Medicines. He receives research support for the study of medicines in children from the UK National Institute of Health Research.

Dr Jacqueline Deen served as a paid consultant to GlaxoSmithKline to develop a training module until May of 2008. Her employer, the International Vaccine Institute receives funding from the Bill and Melinda Gates Foundation, other foundations and vaccine producers. Dr Deen is currently an investigator in a malaria trial conducted in Africa and funded by the Wellcome Trust.

Professor Dai Yao Hua and Dr Elizabeta Zisovska reported no conflict of interest.

Dr Shalini Sri Ranganathan was a non-attending Temporary Adviser who reported no conflict of interest.

For the purposes of this declaration, the participants noted that many of them worked in departments that received funding from other commercial entities but they were not directly involved in these projects. Several participants have held positions in academic or learned societies that have provided general direction on matters pertinent to child health.

## Annex 2: Essential Medicines List for Children

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## **Annex 3: The Anatomical Therapeutic Chemical (ATC) classification system**

\* Medicine or item name differs slightly from the name used.

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## **Annex 4: Alphabetical list of essential medicines for children (with ATC classification code numbers)**

\* Medicine or item name differs slightly from the name used.

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**Annex 5: List of individuals and institutions sending in comments to the Subcommittee**

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## Annex 6: Essential medicines that can be used in neonates

CORE	
oxygen	<b>Inhalation</b> (medicinal gas). ( <i>Section 1.1</i> )
lidocaine	<b>Injectable solution:</b> 1%; 2% (hydrochloride) in vial. <b>Topical forms:</b> 2% to 4 % (hydrochloride). ( <i>Section 1.2</i> )
diazepam*	<b>Injection:</b> 5 mg/ml in 2-ml ampoule. ( <i>Section 1.3</i> ) * Preparations without benzyl alcohol should be used for neonates.
morphine	<b>Injection:</b> 10 mg (as morphine hydrochloride or morphine sulfate) in 1-ml ampoule. ( <i>Sections 1.3 and 2.2</i> ) <b>Oral liquid:</b> 10 mg (as morphine hydrochloride or morphine sulfate)/5 ml. ( <i>Section 2.2</i> )
paracetamol	<b>Oral liquid:</b> 125 mg/5 ml. <b>Suppository:</b> 60 mg. ( <i>Section 2.1</i> )
epinephrine	<b>Injection:</b> 1 mg (as hydrochloride or hydrogen tartrate) in 1 ml ampoule. ( <i>Sections 3 and 25.1</i> )
calcium gluconate	<b>Injection:</b> 100 mg/ml in 10-ml ampoule. ( <i>Section 4.2</i> )
naloxone	<b>Injection:</b> 400 micrograms (as hydrochloride) in 1-ml ampoule. ( <i>Section 4.2</i> )
phenobarbital	<b>Injection:</b> 200 mg/ml (phenobarbital sodium). ( <i>Section 5</i> )
phenytoin	<b>Injection:</b> 50 mg/ml in 5 ml ampoule (as sodium salt). <b>Oral liquid suspension:</b> 25 mg to 30 mg/5 ml. ( <i>Section 5</i> )
amoxicillin as trihydrate (as sodium salt)	<b>Powder for oral liquid:</b> 125 mg (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml. ( <i>Section 6.2.1</i> )
ampicillin	<b>Injection:</b> 500 mg (as sodium salt) in vial. ( <i>Section 6.2.1</i> )
benzylpenicillin (penicillin G)	<b>Powder for injection:</b> 600 mg (= 1 million IU); (sodium or potassium salt) in vial. ( <i>Section 6.2.1</i> )
cefotaxime	<b>Powder for reconstitution:</b> 500 mg. ( <i>Section 6.2.1</i> )
ceftriaxone <sup>a</sup>	<b>Powder for reconstitution:</b> 250 mg; (as sodium salt) in vial. ( <i>Section 6.2.1</i> ) <sup>a</sup> not in infants <41 weeks corrected gestational age.
cloxacillin	<b>Injection:</b> 500 mg (as sodium salt) in vial. ( <i>Section 6.2.1</i> )
procaine benzypenicillin	<b>Suspension for intramuscular injection</b> 1 g. ( <i>Section 6.2.1</i> )

<b>CORE</b>	
□ erythromycin*	<b>Powder for oral liquid:</b> 125 mg (as stearate or ethyl succinate) in 5 ml. ( <i>Section 6.2.2</i> )
gentamicin	<b>Injection:</b> 10 mg (as sulfate)/ml in 2-ml vial. ( <i>Section 6.2.2</i> ) <b>Solution (eye drops):</b> 0,3% (as sulfate). ( <i>Section 21.1</i> )
fluconazole	<b>Injection:</b> 2 mg/ml in vial. <b>Oral liquid:</b> 50 mg/5 ml. ( <i>Section 6.3</i> )
nystatin	<b>Oral liquid:</b> 50 mg/5 ml or 100 000 IU/ml. ( <i>Section 6.3</i> )
zidovudine	<b>Oral liquid:</b> 50 mg/5 ml. <b>Solution for injection:</b> 10 mg/ml. ( <i>Section 6.4.2.1</i> )
nevirapine	<b>Oral liquid:</b> 50 mg/5 ml. ( <i>Section 6.4.2.2</i> )
phytomenadione	<b>Injection:</b> 1 mg/ml in 5 ml ampoule. ( <i>Section 10.2</i> )
methylrosanilinium chloride (gentian violet)	<b>Aqueous solution:</b> 0.5%. ( <i>Section 13.2</i> )
oral rehydration salts	<p>glucose: 75 mEq sodium: 75 mEq or mmol/l chloride: 65 mEq or mmol/l potassium: 20 mEq or mmol/l citrate: 10 mmol/l osmolarity: 245 mOsm/l glucose: 13.5 g/l sodium chloride: 2.6 g/l potassium chloride: 1.5 g/l trisodium citrate dihydrate: 2.9 g/l</p> <p>+ trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use. (<i>Sections 17.5.1 and 26.1</i>)</p>
antitetanus immunoglobulin	500 IU vial. ( <i>Section 19.2</i> )
caffeine citrate	<b>Injection:</b> 20 mg/ml (equivalent to 10 mg caffeine base/ml). <b>Oral liquid:</b> 20 mg/ml (equivalent to 10 mg caffeine base/ml). ( <i>Section 25.2</i> )
glucose	<b>Injectable solution:</b> 10%. ( <i>Section 26.2</i> )
potassium chloride	<b>Solution for injection:</b> 7.5% (equivalent to K 1 mmol/ml and Cl 1mmol/ml). ( <i>Section 26.2</i> )
sodium chloride	<b>Injectable solution:</b> 0.9% isotonic (equivalent to Na <sup>+</sup> 154 mmol/l, Cl <sup>-</sup> 154 mmol/l). ( <i>Section 26.2</i> )

<b>CORE</b>	
water for injection	<b>Solution for injection:</b> 2 ml; 5 ml; 10 ml ampoules. (Section 26.3)
cholecalciferol	<b>Oral liquid:</b> 400 IU/ml. (Section 27)
<b>COMPLEMENTARY</b>	
<i>atropine sulfate</i>	<b>Injection:</b> 1 mg (as sulfate) in 1 ml ampoule. (Sections 1 and 4)
<i>hydrocortisone</i>	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial. (Sections 3 and 8.3)
<i>imipenem + cilastatin</i>	<b>Powder for injection:</b> 250 mg (as monohydrate) + 250 mg (as sodium salt) in vial. (Section 6.2.1)
<i>metronidazole</i>	<b>Injection:</b> 500 mg in 100-ml vial. (Sections 6.2.2 and 6.5.1)
<i>vancomycin</i>	<b>Powder for injection:</b> 250 mg (as hydrochloride) in vial. (Section 6.2.2)
<i>amikacin</i>	<b>Solution for injection:</b> 50 mg/ml. (Section 6.2.4)
<i>aciclovir</i>	<b>Solution for injection:</b> 250 mg/10 ml. (Section 6.4.1)
<i>amphotericin B</i>	<b>Injection:</b> 50 mg in vial. (Section 6.5.2)
<i>digoxin</i>	<b>Injection:</b> 100 micrograms/ml. <b>Oral liquid:</b> 50 micrograms/ml. (Section 12.4)
<i>dopamine</i>	<b>Injection:</b> 40 mg/ml as hydrochloride in 5-ml vial. (Section 12.4)
<i>ranitidine</i>	<b>Injection:</b> 25 mg/ml in 2-ml ampoule. (Section 17.1)
<i>insulin</i>	<b>Injection:</b> 100 IU/ml in 10-ml vial. (Section 18.5)