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A response to the Unedited Report of the First Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

Introduction

HAI welcomes the overriding aim of the selection of essential medicines for children as a contribution to the improvement of global public health, specifically in children. However, the selection of essential medicines for children outlined in the un-edited report of the first meeting of the subcommittee of the Expert Committee on the Selection and Use of Essential Medicines raises some concerns. We observe that an inappropriate number of applications and reviews of the list submitted to the coming Expert Committee meetings seem to be driven by the agenda of pharmaceutical industry rather than one that prioritises public health needs. That said, HAI, a completely independent organisation which is free of any conflicts of interest, would like to draw attention of the Expert Committee members to the following key points.

1. Definition of Essential Medicines for children

Will the definition of 'Essential medicines' be different in the case of children or will it remain the same? HAI believes the definition needs to remain the same.

Quoting the resolution "Better Medicines for children" (**EB120.R13)** that requested the Director General

> "(1) to promote the development, harmonization and use of standards for clinical trials of medicines for children; **to**

> **revise and regularly update the Model List of Essential Medicines in order to include missing essential medicines for children,** using evidence based clinical guidelines; and to promote application of such guidelines by Member States and international financing bodies, with initial focus on treatments for HIV/AIDS, tuberculosis, malaria and chronic diseases;"

and quoting the terms of reference for a temporary Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines:

> "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"

and recognising that the existing WHO Model List of Essential Medicines already covers some essential medicines for children, we believe that any proposed suggestions for changes contained in the Unedited Report should meet criteria identical to any (WHO Model List) list issue, i.e. the same definition of essential medicines and selection procedures are to be applied. In light of this, some of the proposed applications raise concern: for a non-sedating antihistamine; a proton-pump inhibitor; domperidone to replace metoclopramide; a 5HT3 antagonist for nausea; lactulose; risperidone and other medicines for different psychiatric disorders; anti-asthmatics such as an anti-cholinergic agent and a long-acting beta-agonist.

2. Technical considerations on the structure of the proposed EMLc

A) Moving medicines to a complementary list in the proposed EMLc does not seem to follow the original (and stated in the report) definition of complementary listing:

> "The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings."

Some examples from the proposed EMLs include spironolactone, hydrochlorothiazide, mannitol, acetylsalycilic acid, neostigmine, etc. The question is why would hydrochlorothiazide require more monitoring or special medical care than furosemide?

B) Square box symbols.

We do not understand why these have to be applied to medicines other than on the existing WHO Model EML 15. Some examples with deleted square box symbols include haloperidol and chlorpromazine, etc.

3. Construction of a separate EMLc

Factors that argue against construction of a separate EMLc include the following:

- The disease burden for the majority of sections of the EMLc has not been defined precisely.
- Clinical trial data is an insufficient basis for a rational decision making process,
- Emerging Drug utilization and pharmacovigilance data must be taken into account.
- Too many sections need to be reviewed (31 reviews requested), and for the majority of requested reviews, data are still lacking.

The current EMLc, approved by the Subcommittee, presents a framework for future deliberation and should not be used as a list in its own right.

HAI strongly believes that **a conservative approach for identifying new and missing essential medicines provides the greatest benefit for public health and even more so for children's health.** The majority of the most common diseases in children such as upper respiratory tract infections and diarrhoea are often self-limiting and do not require medicines use. This needs to be outlined in the preamble to the list and in the report. Listing of non-essential medicines can lead to misuse and overuse of medicines in children and result in increased iatrogenic problems.

We present just two examples, which prioritise children's health needs over the interests of the pharmaceutical industry that require consideration by the Expert Committee members:

Midazolam

(Section 1.3 Preoperative medication and sedation for short-term procedures)

There is little public health need and no evidence for suggesting midazolam be preferable to diazepam for this indication. Although there is no data on a direct comparison of midazolam and diazepam there are 2 Cochrane reviews on effects of midazolam in neonates[1,2]. The review "*Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit*" (3 trials, 146 participants) concluded intravenous midazolam infusion **should not be recommended** due to safety concerns. The review found an upward trend in risk of intracranial hemorrhage (any grade) with midazolam use over placebo (P=0.1), Relative Risk of 1.68 with 95% Confidence Intervals from 0.87 to 3.24. Meta-analysis of the data from two included trials (Jacqz-Aigrain 1994[3] and Anand 1999[4]) showed that the midazolam group had a statistically significantly longer length of stay in the NICU than the placebo group (WMD 5.4 days, 95% CI 0.4, 10.5).

The second Cochrane systematic review "*Opioids for neonates receiving mechanical ventilation*"[5] recommended morphine over midazolam for pain relief because of fewer adverse effects on the basis of one included trial (46 participants).

The review found a statistically significant increased risk of any intraventricular haemorrhage with midazolam (comparison morphine versus midazolam, RR 0.28; 95% CI 0.09 to 0.87); longer duration of mechanical ventilation with midazolam (Days, Weighted Mean Difference -6.7; 95%CI -12.40 to -1.0) and prolonged hospital stay with midazolam (Days, Weighted Mean Difference -21.90; 95%CI -43.56 to -0.24).

Such data do not exist for diazepam. The issue on preferential benzodiazepine for preoperative use and sedation for short-term procedures, if to be discussed at all, needs to be discussed for the major list – WHO Model EML.

Midazolam and diazepam produce similar degrees of hypoventilation and oxygen desaturation when used in equivalent doses[6], however the sedative end-point does appear to be reached more abruptly with **midazolam**[7]. This is the reason for the need for appropriate precautions, such as resuscitation equipment, to be always available when intravenous **midazolam** is used; respiratory and cardiac function be monitored continuously; the dose of **midazolam** to be carefully titrated against the response of the patient, and the manufacturer's recommendations, concerning speed of administration, be observed particular care, including a reduction in **midazolam** dosage, is required in patients also receiving opioid analgesics, in the elderly and children, and in patients with compromised cardiorespiratory function[8]

Promethazine was not endorsed because of the risk of respiratory depression in children under 2 years of age. The question arises: what is the comparative risk of respiratory depression with promethazine versus midazolam? (Phenothiazines vs benzodiazepines).
Noteworthy are the findings of the Cochrane systematic review (2 high quality trials, 501 participants)[9] on midazolam and lorazepam to be associated with respiratory depression when compared to combination of haloperidol and promethazine in acute psychotic patients with aggression.

In conclusion, midazolam should not be considered as preferable alternative to diazepam in section 1.3.

Antihistamines

Section 3. Antiallergics and medicines used in anaphylaxis.

Review and preparation of application for a non-sedating antihistamine for use in children was suggested.
The question arises: what is the value of sedating versus non-sedating antihistamines? Do different dosage forms really need to be available? Children under 2 years of age – is there evidence of effects?
There is accumulating evidence from Cochrane reviews about the lack of clinically meaningful beneficial effects of antihistamines, both sedating and non-sedating, in the most common childhood (and adult) conditions:

- For an acute cough in children and adults (sedating and non-sedating antihistamines used: brompheniramine maleate, dexbrompheniramine, chlorpheniramine maleate, clemastine fumarate, loratadine and terfenadine).[10]

- For common cold in children and adults (35 trials involving 8930 participants, sedating and non-sedating antihistamines used)[11]. Any further trials of antihistamines in common cold including non-sedating antihistamines are not justified.

- For otitis media with effusion in children (recommendation against antihistamines, antihistamine/decongestant combinations' use and no need for future research concluded by the authors; the review found no benefit whatsoever and increased risk of adverse effects by 11%)[12]

- For acute otitis media in children (recommendation against antihistamine use)[13]

- For preventing a reaction to snake antivenom in children over 2 years and adults (promethazine as premedication before antivenom)[14]

- For symptomatic treatment of cough in whooping cough (1 trial involving 49 participants under 1 year of age with bacteriologically diagnosed pertussis, diphenhydramine)[15]

- For prolonged non-specific cold in children (3 trials involving 182 participants, sedating and non-sedating antihistamines used)[16]

In conclusion, there is no need for preparation of application for a non-sedating antihistamine; it will not qualify for essentiality criteria.

On the basis of these observations we propose to:

a. Maintain the unique WHO Model EML with its principles and structure including complementary listing and square box symbols.

b. Strictly follow criteria of essentiality when considering adding a new medicine to the WHO Model EML.

c. Incorporate only those very few missing evidence-supported medicines/formulations/dosage forms for children and outline priority research issues in the footnotes.

d. Identify listed medicines/formulation/dosage forms not to be used in children or in children of certain age groups and clearly mark these on the WHO Model EML

e. Stand strong to the marketing pressure of developing WHO Model Formulary for children.

References:

[1] E Ng, A Taddio, A Ohlsson. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD002052. DOI: 10.1002/14651858.CD002052.

[2] R Bellù, KA de Waal, R Zanini. Opioids for neonates receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004212. DOI: 10.1002/14651858.CD004212.pub2

[3] Jacqz-Aigrain E, Daoud P, Burtin P, Desplanques L, Beaufils F. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. Lancet 1994;**344**:646-50.

[4] Anand KJS, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. Analgesia and sedation in preterm neonates who require ventilatory support - results from the NOPAIN trial. Arch Pediatr Adolesc Med 1999;**153**:331-8.

[5] R Bellù, KA de Waal, R Zanini. Opioids for neonates receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004212. DOI: 10.1002/14651858.CD004212.pub2

[6] Bell GD. Review article: premedication and intravenous sedation for upper gastrointestinal endoscopy. *Aliment Pharmacol Ther* 1990; **4:** 103–22. PubMed

[7] Ryder W, Wright PA. Dental sedation: a review. *Br Dent J* 1988; **165:** 207–16. PubMed

[8] Martindale: The Complete Drug Reference, CD-Rom version, 2005.

[9] G Huf, J Alexander, MH Allen. Haloperidol plus promethazine for psychosis induced aggression. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD005146. DOI: 10.1002/14651858.CD005146.

[10] K Schroeder, T Fahey. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub2.

[11] AIM De Sutter, M Lemiengre, H Campbell. Antihistamines for the common cold. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001267. DOI: 10.1002/14651858.CD001267.

[12] GH Griffin, C Flynn, RE Bailey, JK Schultz. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD003423. DOI: 10.1002/14651858.CD003423.pub2.

[13] CA Flynn, GH Griffin, JK Schultz. Decongestants and antihistamines for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD001727. DOI: 10.1002/14651858.CD001727.pub3.

[14] Nuchpraryoon, P Garner. Interventions for preventing reactions to snake antivenom. *Cochrane Database of Systematic Reviews* 1999, Issue 4. Art. No.: CD002153. DOI: 10.1002/14651858.CD002153.

[15] V Pillay, G Swingler. Symptomatic treatment of the cough in whooping cough. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD003257. DOI: 10.1002/14651858.CD003257.

[16] AB Chang, J Peake, MS McElrea. Anti-histamines for prolonged non-specific cough in children. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD005604. DOI: 10.1002/14651858.CD005604.pub2.