Subject: FW: Comments on Report of 1st meeting of paediatric subcommittee of expert committee on selection and use of essential medicines

From: Madlen Gazarian [mailto:MADLEN.GAZARIAN@]
Sent: 11 October 2007 08:05
To: Hill, Suzanne
Cc: emlsecretariat
Subject: Comments on Report of 1st meeting of paediatric subcommittee of expert committee on selection and use of essential medicines

Dear Sue

I am writing to make some general comments about the July EMLc meeting report as well as a few specific comments on one section of the draft list itself. I hope that the Expert committee will find these helpful for their deliberations at the October meeting.

GENERAL COMMENTS:

1. ***Approach to identifying priority paediatric health needs at a global level:***

I acknowledge that the pragmatic starting point for this draft list was the existing (general) EML, rather than a delineation of the priority diseases affecting the paediatric population globally (eg as defined by epidemiological data re disease burden). The paediatric sub-committee has already identified that this approach has meant some essential or priority paediatric health needs are currently not addressed by the draft list. The committee and the Secretariat are to be commended for their efforts in identifying some of these obvious gaps at the July meeting and seeking further input to identify additional important gaps since then. This is obviously an especially important step to get right, particularly in view of the planned linkage to prioritisation of areas for further research.

My main comment is that the relatively short time-frame within which this feedback is being sought from around the globe will mean that not all relevant stakeholders (at country and regional level) will have had an opportunity to engage with the process in a meaningful way. I have circulated the request for feedback through some paediatric professional networks and interested colleagues in Australia and New Zealand, but suspect the request may not yet have filtered through to all the relevant individuals or groups. We are likely to be undertaking our own local process in the near future to identify priority paediatric medicines needs in Australia and would be happy to convey that information to the EMLc secretariat in due course if that would be helpful.

A related comment is that identification and prioritisation of relevant gaps will be different depending on whether the perspective is from that of the developing or the developed world, and will also vary between regions within this broad categorisation. If the intention is that the EMLc will ideally address the needs of all regions (eg as

suggested in your Editorial in the Bulletin of the WHO in Sep 07), then an additional point to raise is whether separate prioritisations of needed research for the developing and the developed world might be appropriate to consider (although there will obviously be some commonalities)?

2) Approach to assessing whether there is "sound and adequate data on the efficacy, safety and comparative cost-effectiveness of available treatments":

Clearly this is one of the existing criteria for an "essential medicine". I have noted the paediatric sub-committee's interpretation (as described on page 12 of the July meeting report) being that marketing authorisation by a competent authority would be considered sufficient to meet this criterion. I suggest that licensing by a competent regulatory authority (eg FDA, EMEA) might be considered useful but not sufficient to meet this criterion in all cases, as discussed on page 13 of my paper which was part of the background papers for the July meeting: http://mednet3.who.int/EML/expcom/CHILDREN/INDEX_children_07.htm

Some specific points to expand further:

- Where there are no currently available alternatives to treat a particular priority paediatric condition, licensing by a competent authority is reasonable as a starting point for listing on the EMLc. However, given the well-recognised limitations of such data for informing therapeutic decision-making in all clinical contexts, additional evidence will be needed (eg data on longer term effectiveness and safety for medicines intended to be used long term, especially in younger children) to justify ongoing listing on EMLc for such uses. So, I would strongly urge that the approach suggested on page 17 of my paper, similar to the "conditional approval" models currently being recommended for regulatory assessment of medicines, be considered further by the committee and linked to the research agenda in an ongoing fashion.

- Where there is an existing medicine listed on the EMLc and an alternative is being considered, then licensing by a competent authority is not sufficient to meet this criterion. Information on comparative effectiveness, safety and cost-effectiveness are not part of drug regulatory agencies' assessments for marketing approval and need to be sought from other sources (see page 13, para 1 and 4, and page 17 for more on these points). In many instances studies to generate this type of evidence are entirely feasible to conduct in the paediatric population but are often not undertaken because of lack of appropriate drivers and resourcing for such research. Incorporating this requirement here should help to steer the evolving global paediatric medicines research agenda in a direction that will better meet the information needs of decision-makers, and ultimately should lead to improved health outcomes in the paediatric population (see point 4, page 11 of my paper).

- The recommendations for evidence evaluation outlined in section 6 (pages 13-18) of my paper are intended to apply broadly to evaluating the

suitability of any essential medicines proposed for addition to the EMLc, irrespective of registration status. The basic tenet is that it should be the availability of relevant **evidence** (as described), not the registration status in a particular country or region, that should determine suitability of a medicine's addition to the EMLc and/or define needed areas of further research for different clinical or public health needs. Such decisions by the paediatric subcommittee could then help inform decision-making at country level (eg re seeking regulatory approval or decisions about public subsidy etc, if these aren't already in place). This would strengthen the EMLc's usefulness as a global policy and advocacy tool as suggested in your Editorial.

I'm pleased to note that the committee found the overall framework helpful in their decision-making process. However, there seems to have been some variability between individual experts' interpretation and application of the framework to individual drugs. For example, artesunate suppositories were supported for listing, even though it was acknowledged that these were not yet "approved by a stringent regulatory authority or the WHO Prequalification Programme". However, terbinafine was rejected apparently due to its lack of licensing, despite data (at least as described in the meeting report) suggesting superiority to available alternatives in some aspects. I may be misinterpreting what might have been meant here, but some clarification and consistency in this regard would be very helpful.

I would also suggest that some discussion of the general issues raised on page 19 of my paper (especially 1, 2, 3) would also be useful. I'm happy to expand on or clarify any points as needed.

3) Needs of children aged over 12 years:

It is noted on page 12 of the July meeting report that these children can generally use dosage forms designed for adults, which is true for the majority of this age group. However, paediatric patients with significant developmental delay or neurological abnormalities may have difficulty ingesting adult dose forms on a long term basis. Such children/adolescents would need to have access to alternative formulations (eg liquids) regardless of their chronological age.

Independent of the dosage form issue, the need to obtain evidence for the effectiveness and safety of new medicines in this age group also needs to be considered; eg as highlighted by the relatively recent controversy about SSRIs and possibly increased risk of suicidality specifically in this population.

4) Needed evidence reviews identified for specific medicines:

It would be important to avoid possible duplication of effort here. Various paediatric and non-paediatric organisations may have already undertaken (or be in the process of preparing) some of the reviews identified. I'm aware of some but obviously not all of these. Examples include:

· Cochrane Child Health field: eg involved in preparation of systematic reviews of ibuprofen and paracetamol for various indications in the paediatric population (in collaboration with the Cochrane Infectious Disease and International Health group based in UK). Some of these are not necessarily on the electronic database. If you haven't already done so, it may be worth contacting the Child Health field people directly to identify any other relevant reviews or protocols. I can send contact details if needed.

· NICE in the UK: eg have a number of evidence reviews on areas the committee has identified; eg newer agents for the management of epilepsy, asthma etc in children.

· Agency for Health Care Research and Quality (AHRQ) in the US: eg currently undertaking some major work in evaluating the evidence around the safety of medicines used to treat ADHD in children.

If you haven't already done so, it might be useful to approach these and similar organisations undertaking major evidence reviews to see if some of the areas of work the EMLc sub-committee has identified may already be addressed, at least in part.

5) Research needs:

I note that the only area currently listed here is that of ototoxicity of gentamicin. We have just completed some research in this area at my own institution which I would like to draw your attention to. The research was undertaken by one of my students (Dr Emma Best) as part of a Master of Medicine degree at UNSW, which has just been completed. The manuscript for publication in the peer-reviewed literature is currently under preparation. Details of the thesis are given below, as well as a letter to the Editor of Pediatrics with some pertinent details.

- *Best E (2007) 'Once daily gentamicin in children: an evaluation of safety and the role of therapeutic drug monitoring in minimising toxicity' (MMed) University of New South Wales*

- *Best EJ, Palasanthiran P, Gazarian M. Extended-Interval aminoglycosides in children: More guidance is needed. Pediatrics 2005;115:827-828*

  http://pediatrics.aappublications.org/cgi/content/full/115/3/827-a

Areas which aren't addressed by the above work are the ototoxicity of single daily dosing of gentamicin in neonates and some other high risk populations. So, these remain important areas of needed research for this particular dosing regimen for gentamicin, which seems to be gaining increasing popularity in paediatric practice.

SPECIFIC MEDICINES

Section 2: I suggest that the title and content of this section might be better to divide into two separate sections. My suggestion is along the lines of:

a) Analgesics and antipyretics; and

b) Non-steroidal anti-inflammatory medicines (NSAIMs) and medicines for the treatment of rheumatic disorders, including DMARDS

[PS: I note that section 17.3 “Anti-inflammatory medicines” has been deleted. I’m not sure that I understand the reasoning for this decision, as outlined below]

NSAIMs (or NSAIDs) and DMARDS are the mainstays of treatment for a wide variety of rheumatic disorders in the paediatric age group. These include the various types of juvenile arthritis but also extend to various connective tissue diseases as well; SLE and vasculitis being just some examples. My previous comment about JIA prevalence was only to highlight the issue of prevalence of that disorder in this overall group. I suggest that the planned review should address both the prevalence of this overall group of disorders in the developing world as well as essential medicines to treat the range of disorders, rather than being limited to JIA alone. In fact, some populations in the developing world have considerably higher incidence and prevalence (vs developed world populations) of some of the connective tissue diseases (eg SLE), with significant disease burden, and so this group of diseases should be appropriately addressed by the EMLc.

In terms of the role of acetylsalicylic acid, as discussed in the NSAIDs paper I had submitted previously,
http://mednet3.who.int/EML/expcom/CHILDREN/LATE/NSAIDskidsMedToday.pdf

there are much better alternatives now available for NSAID treatment of JIA or other chronic inflammatory conditions. Naproxen has been widely used for this purpose for many years now, and in fact is currently the only liquid NSAID listed for public subsidy on the Australian Pharmaceutical Benefits Scheme. I realise that naproxen is currently not listed on the EMLc, but hopefully this information will come out in the review of the overall section that you are planning. While ibuprofen may be used also to treat chronic inflammatory conditions, it has a number of drawbacks (including need for 3 or 4 times a day dosing) which limits its usefulness for chronic treatment. I also note that a liquid form of ibuprofen is not on the draft EMLc, which would be needed for treatment of younger children with rheumatic disorders, and should be noted if the committee decides to extend the use of ibuprofen for this indication rather than seeking the addition of another NSAID such as naproxen.

I hope that you find these comments useful and look forward to hearing about the outcome of the October meetings. Please let me know if you need any further information or clarification about any of the points I have raised.

Best wishes

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