Expert peer review on application for CHLORHEXIDINE for umbilical cord care

This application has been submitted by PATH on behalf of the Chlorhexidine Working Group requesting a change in the from the current listing of ‘Chlorhexidine Solution: 5%(digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care)’ to:

7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine for umbilical cord care

A similar proposal was consider in 2011, but was not approved, as at that time there was no commercially available product of the appropriate concentration.

1. Assessment of efficacy

a. Have all relevant studies on efficacy been included

Yes No (if no, please provide reference and information)

The application does not present the studies, but refers to an upcoming WHO guideline that follows a meeting in September 2012. *As the guideline is not yet published (as of Feb 28 2013) the data presumably will be made available to the Committee.*

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The Chlorhexidine Working Group website lists 3 trials and an unpublished meta-analysis:


Average mortality reduction of cord cleansing with 7.1% chlorhexidine digluconate (4% free chlorhexidine) from research studies. Un-published meta-analysis; Chlorhexidine Working Group.

The website does not provide complete data, but based on the published trials, the table below has been constructed. The published trials do not report absolute estimates of effect.
### Neonatal mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Dry Cord Care</th>
<th>Soap and Water</th>
<th>Chlorhexidine</th>
<th>Chlorhexidine + Handwashing</th>
<th>Relative Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullany 2006</td>
<td>90/5082</td>
<td>98/5107</td>
<td>72/4934</td>
<td>---</td>
<td>0.76 (0.55, 1.04)</td>
</tr>
<tr>
<td>Soofi, 2012</td>
<td>81/2399</td>
<td>95/2475</td>
<td>66/2653</td>
<td>45/2214</td>
<td>0.62 (0.45, 0.85)</td>
</tr>
<tr>
<td>El Arifeen, 2012</td>
<td>238/10008</td>
<td>---</td>
<td>212/9423</td>
<td>275/10329</td>
<td>0.80 (0.65, 0.98)</td>
</tr>
</tbody>
</table>

### Omphalitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Dry Cord Care</th>
<th>Soap and Water</th>
<th>Chlorhexidine</th>
<th>Chlorhexidine + Handwashing</th>
<th>Relative Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullany 2006</td>
<td>638/5082</td>
<td>660/5107</td>
<td>438/4934</td>
<td>---</td>
<td>0.25 (0.12, 0.53)</td>
</tr>
<tr>
<td>Soofi, 2012</td>
<td>182/2399</td>
<td>127/2475</td>
<td>84/2653</td>
<td>82/2214</td>
<td>0.53 (0.32, 0.88)</td>
</tr>
<tr>
<td>El Arifeen, 2012</td>
<td>42/994</td>
<td>---</td>
<td>31/9354</td>
<td>16/10254</td>
<td>0.77 (0.40, 1.48)</td>
</tr>
</tbody>
</table>

1. Chlorhexidine vs dry cord care
2. Compared single vs multiple cleansing with chlorhexidine vs dry cord care
3. Single cleansing group
4. Multiple cleansing group
5. Based on ‘definition 1’ as report in publication
6. Reported as ‘severe redness with pus’
7. For single use vs dry cord care

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c. Please provide any additional relevant information with reference

NA

### 2. Assessment of safety

a. Have all relevant studies on safety been included
   
   **Yes** | **No** (if no, please provide reference and information)

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Topical chlorhexidine has been used as a disinfectant for many years and has few adverse effects when used in concentrations as proposed in this application. The trials note the possible increase in cord separation time in those neonates who had chlorhexidine cord care, but the clinical significance of this finding is unclear.

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c. Please provide any additional relevant information with reference

NA

### 3. Assessment of cost and availability

a. Have all relevant data on cost and availability been provided
   
   **Yes** | **No** (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Topical chlorhexidine in the appropriate concentration is very cheap. Estimates of cost–effectiveness are provided in the application.
c. Please provide any additional relevant information with reference

NA

d. Is the product available in several low and middle income countries?

At the last EML Committee meeting in 2011, the appropriate concentration of chlorhexidine for cord care, as used in the trilas, was not available as a commercial product. There are now at least 2 suppliers: one from Nepal and one from India. The UNICEF comment on the application suggests that more suppliers will emerge if demand increases.

The application makes the point that for this product, local manufacture will be the most appropriate source. Quality standards will need to be enforced to ensure that the appropriate concentrations are provided.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

Neonatal sepsis is one of the major causes of neonatal mortality. While the trials do not report sepsis specific deaths, the effect of chlorhexidine cord care on all-cause mortality is significant. Interventions to reduce neonatal mortality clearly meet a significant public health need.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

There is an update WHO guideline due to be published, according to the application.

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

NO.

6. Is the proposed product registered by a stringent regulatory authority?

Yes  No  See comments concerning source of supply, above.

7. Any other comments

NA

8. What is your recommendation to the committee (please provide the rationale)

The Committee should amend the EML as proposed for chlorhexidine.