MEMORANDUM

November 30, 2012

TO: World Health Organization Expert Committee on the Selection and Use of Essential Medicines

FROM: PATH, on behalf of the Chlorhexidine Working Group

RE: Change requested in the next World Health Organization Model List of Essential Medicines for Children 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 |

Background

The 2011 World Health Organization (WHO) Model List of Essential Medicines for Children (EMLc) includes chlorhexidine for umbilical cord care under section 15. DISINFECTANTS AND ANTISEPTICS, subsection 15.1. Antiseptics. The listing is as follows:

Chlorhexidine

Solution: 5% (digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care)

The 17th Expert Committee on the Selection and Use of Essential Medicines convened by WHO in 2009 concluded that data from a community-based, cluster-randomized controlled trial (RCT) in Nepal showed a significant reduction in neonatal mortality after use of a 4% chlorhexidine solution (7.1% chlorhexidine digluconate) for umbilical cord care. This was sufficient to include such a product and indication for use in the WHO EMLc. Nevertheless, due to the absence of a commercially available 4% chlorhexidine (7.1% chlorhexidine digluconate) product at that time, this recommendation of the expert review committee resulted in listing 20% chlorhexidine (digluconate) with an instruction to dilute for umbilical cord care use. At the time of publication of the March 2009 WHO model list, PATH and the US Agency for International Development submitted joint letters3 (http://www.who.int/entity/selection_medicines/committees/expert/17/application/paediatric/PATH_chlor_paed.pdf and http://www.who.int/entity/selection_medicines/committees/expert/17/application/paediatric/USAID_Chlor_paed.pdf) to the WHO expert review committee stating that the indication was not clear and suggesting that it should be revised to stipulate use of 4% chlorhexidine for umbilical cord care. WHO responded by saying that such an issue would be taken up during the next review of the EMLc in 2010–2011.

In 2010, PATH submitted an amendment4 (http://www.who.int/entity/selection_medicines/committees/expert/18/applications/chlorhexidine_app.pdf) with additional data to the WHO expert review committee to support the clarification of the indication for use of chlorhexidine for umbilical cord care by stipulating use of 4% chlorhexidine in either gel or aqueous solution. The expert committee decided to maintain the previous listing for chlorhexidine until a product of the strength and formulation used...
the trials is commercially available (i.e., availability of the product on the open market, not just for trial purposes). Specifically, the Final Report of 18th Expert Committee on the Selection and Use of Essential Medicines (21 to 25 March, 2011)\(^5\) noted that:

“The problem remains that, as in 2009, a commercially available preparation of 7.1% chlorhexidine digluconate solution or gel (delivering 4% chlorhexidine) is not yet available. While the 20% requires dilution and manipulation and is clearly not optimal, until there is a commercially available product of the strength and formulation used in the trials, the current listing cannot be amended. However, the Committee noted that an optimized 4% chlorhexidine is listed as one of the priority products for development by WHO on the Priority Medicines list for maternal and child health and therefore flagged it as a ‘missing’ essential medicine, given the impact on mortality suggested in the trials.”

It is critical to clarify use of the language “7.1% chlorhexidine digluconate, delivering 4% chlorhexidine for umbilical cord care” because there is very common confusion regarding the concentrations of chlorhexidine digluconate versus chlorhexidine. The conversion between the two is listed in Table 1 below. It is important to note that the current EMLc listing of 5% chlorhexidine digluconate delivers only approximately 2.8% chlorhexidine, a lower level than what was used in the RCTs for umbilical cord care. If decision makers are not aware of the difference between chlorhexidine digluconate and chlorhexidine, they might assume that the “5% chlorhexidine (digluconate)” listed on the EMLc is higher than 4% chlorhexidine and therefore any in-country regulatory process is not necessary—an incorrect assumption.

**Table 1. Chlorhexidine digluconate versus chlorhexidine.**

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<thead>
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<th>Chlorhexidine Digluconate</th>
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To avoid this confusion between chlorhexidine digluconate and chlorhexidine, the EMLc should state:

**Chlorhexidine**

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

The information contained in the attached application is meant to update the existing product dossier that was submitted to the Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines held in Geneva during 29 September to 3 October, 2008. The existing dossier is titled “Review of the available evidence on 4% chlorhexidine solution for umbilical cord care for the WHO Model List of Essential Medicines” and can be accessed at: [http://www.who.int/selection_medicines/committees/subcommittee/2/chlorhexidine.pdf](http://www.who.int/selection_medicines/committees/subcommittee/2/chlorhexidine.pdf). We ask the Expert Committee to refer to the 2008 product dossier for detailed background information on the 7.1% chlorhexidine digluconate product for umbilical cord care.
Application for change of a medicine in the next Model List of Essential Medicines for Children

1. Summary statement of the proposal for inclusion, change or deletion.

Change requested in the next World Health Organization Model List of Essential Medicines for Children from the current listing of Chlorhexidine Solution: 5% (digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care) to:

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2. Name of the focal point in WHO submitting or supporting the application (where relevant).

3. Name of the organization(s) consulted and/or supporting the application.

This request for revision is supported by the Chlorhexidine Working Group (CWG). The CWG is an international collaboration of organizations committed to advancing the use of 7.1% chlorhexidine digluconate (4% chlorhexidine) for umbilical cord care through advocacy and technical assistance. The CWG includes individuals from the US Agency for International Development, PATH, MCHIP, JSI, Johns Hopkins Bloomberg School of Public Health, Save the Children/Saving Newborn Lives program, the Bill & Melinda Gates Foundation, UNICEF Programme Division, UNICEF Supply Division, PSI, United States Pharmacopoeia/Promoting the Quality of Medicines in Developing Countries project, Management Sciences for Health, Boston University, Jhpiego, and Venture Strategies Innovations.
4. **International Nonproprietary Name (INN, generic name) of the medicine.**

Chlorhexidine

Chlorhexidine gluconate/digluconate* is listed by the United States Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia as an aqueous solution containing 20% chlorhexidine digluconate.

5. **Formulation proposed for inclusion; including adult and paediatric (if appropriate).**

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

6. **International availability—sources, if possible manufacturers and trade names.**

Chlorhexidine for umbilical cord care comes in both gel and liquid forms. The 7.1% chlorhexidine digluconate gel is currently available under the trade name of “Kawach” from Lomus Pharmaceuticals in Nepal. Lomus has certification of Good Manufacturing Practice (GMP) from the local government. Website: [http://www.lomus.com.np/](http://www.lomus.com.np/). Email: info@lomus.com.np.

Lomus has registered the product with the Department of Drugs Administration in Nepal, and 7.1% chlorhexidine digluconate is on Nepal’s national essential medicines list for 2011 as a solution or gel for umbilical cord care.

UNICEF sourced the liquid solution from Galentic Pharma Pvt. Ltd. (Mumbai, India), which will soon be available through the UNICEF supply division catalogue; please see: [https://supply.unicef.org/](https://supply.unicef.org/).

The demonstration of commercial availability of 7.1% chlorhexidine digluconate is addressed, in part, by the current practice for bracketing and matrixing designs for stability testing of drug substances and drug products. The International Conference on Harmonization Tripartite Guideline on Stability Testing of New Drug Substances and Products [Q1A(R2): [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf)] matrixing and bracketing can be applied, if justified, to the testing of new drug substances and products to confer stability, shelf life, and hence ultimately availability of the said medication. Further, the European Medicines Agency note for guidance on bracketing and matrixing (CPMP/ICH/4104/00: [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002652.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002652.pdf)) section 2.3.1 states “Bracketing can be applied to studies with multiple strengths of identical or closely related formulations...With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

Therefore, commercial availability of 7.1% chlorhexidine digluconate can be implied by commercial availability of quality 20% and 5% chlorhexidine through bracketing. Both 20% chlorhexidine and 5% chlorhexidine are in WHO EML.

Furthermore, in 2012 UNICEF Supply Division has successfully procured 7.1% chlorhexidine digluconate from Galentic Pharma (India) and has established a long-term arrangement with this supplier to

* NOTE: It is common practice to use “chlorhexidine gluconate” and “chlorhexidine digluconate” interchangeably when referring to the concentrated chemical antiseptic; the pharmacopoeias usually list both names and cross reference to the other. “Chlorhexidine digluconate” is used throughout this document for precision and consistency.
continue supplying 7.1% chlorhexidine digluconate for cord care. In addition to Galentic, Purna Pharma (Belgium) and Sirmaxo Pharma (India) are also suppliers of 5% chlorhexidine through UNICEF Supply Division. Both Purna and Sirmaxo indicate their willingness to start producing 7.1% chlorhexidine digluconate when demand for this product increases.

Further, the CWG is encouraging local manufacture of chlorhexidine for umbilical cord care to increase product availability. Local production is defined as production in low- and middle-income countries (LMICs) by locally owned companies or subsidiaries of multinational companies. The benefits of local production include improvement in reliability of supply, foreign import savings, development of further innovation capacity, creation of enhanced export capacity, and development of human capital. Local production could also lead to cost savings and improvement in product quality, depending on the product to be produced and regular surveillance of LMICs’ quality control issues. Furthermore, local production creates more favorable conditions for the development of products adapted to local cultural preferences.

The product profile of 7.1% chlorhexidine digluconate is conducive to local production. Many LMICs also have pharmaceutical industries capable of locally producing this medicine because:

- 7.1% chlorhexidine digluconate for cord care does not require a proprietary active pharmaceutical ingredient (API), equipment, or process for manufacturing. There is no intellectual property restricting the raw materials, formulation, or production process.
- Pharmaceutical companies in many LMICs are capable of secondary production (i.e., the production of finished dosage forms from raw materials and excipients) for topical medicines. Thirty-four countries in Africa, for example, indicated that they have secondary-level production.
- The API for 7.1% chlorhexidine digluconate for umbilical cord care—20% chlorhexidine digluconate—is manufactured in multiple countries and is readily available for purchase and import.

Several factors must be taken into account when considering whether local production of 7.1% chlorhexidine digluconate would be the optimal option for LMICs to increase availability of the product at affordable prices. Under certain situations, local production may not be the right choice. These situations include: [1] the pharmaceutical industry in the country is weak, and pharmaceutical manufacturers that are capable of producing quality 7.1% chlorhexidine digluconate cannot be found or [2] the market size for 7.1% chlorhexidine digluconate in the country is too small to justify local production (either the cost to purchase and deliver the API to the country is too high due to the small purchase quantity, or the price of the finished product becomes too high when the production quantity is too small). Under one or more of these circumstances, the alternative would be to establish a production base in another country that already has a relatively strong pharmaceutical industry in its region and then to distribute 7.1% chlorhexidine digluconate regionally.

Product quality must be ensured whether 7.1% chlorhexidine digluconate for cord care is produced locally or regionally. The United Nations Commission for Life-Saving Commodities for Women and Children (UNCoLSC) implementation plan (http://www.everywomaneverychild.org/images/Implementation_plan_Sept_2012.pdf) calls for pharmaceutical companies that manufacture 7.1% chlorhexidine digluconate for cord care to [1] have GMP certificates and [2] purchase the API from quality manufacturers, especially those compliant with the most current GMP (cGMP). In line with this, the quality of 7.1% chlorhexidine digluconate for cord care would be assured through three layers: [1] acquisition of raw materials from quality sources, [2] production of the finished product by GMP-compliant manufacturers, and [3] pre-purchase/sales inspections by third-party laboratories when required.
The supply strategy for this product hinges on local production. In the interim, a one-time waiver for UNICEF product could be secured for six months to one year while local production is being established. The chlorhexidine global implementation plan for the UNCoLSC includes the establishment of local/regional manufacturing of 7.1% chlorhexidine digluconate as one of the primary outcomes for the next year. Specifically, efforts under the UNCoLSC work plan will result in [1] bulk chlorhexidine purchased by local/regional manufacturers from cGMP-compliant manufacturers for local production of 7.1% chlorhexidine digluconate for umbilical cord care product and [2] product registration of 7.1% chlorhexidine digluconate for umbilical cord care obtained by local/regional manufacturers in at least three countries.

7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group.**

This change in the listing refers to an individual medicine.

8. **Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population).**

Each year 3 million newborns die globally, and infection causes approximately 13% of these deaths.8 Lack of hygiene and antisepsis at birth and in the first week of life increases the risk of deadly but preventable infections. Community-based RCTs in rural areas in Nepal, Bangladesh, and Pakistan have shown that applying 7.1% chlorhexidine digluconate (4% chlorhexidine) to the umbilical cord stump prevents infection and saves newborn lives.9,10,11 These trials support chlorhexidine cord cleansing as an efficacious, acceptable, feasible, and cost-effective newborn care intervention.

The UNCoLSC (http://www.everywomaneverychild.org/resources/un-commission-on-life-saving-commodities),12 which is part of the United Nation’s Every Woman Every Child movement (http://www.everywomaneverychild.org), identified chlorhexidine for newborn cord care (http://www.everywomaneverychild.org/component/content/article/1-about/308-chlorhexidine-chx--product-profile-) on its list of 13 affordable, effective, but underutilized life-saving commodities.13 On September 26, 2012, the commissioners of the UNCoLSC submitted a new plan and set of recommendations (www.everywomaneverychild.org/images/UN_Commission_Report_September_2012_Final.pdf) to improve the supply and access of life-saving health supplies—including chlorhexidine—to the UN Secretary-General.14

The effect size has varied across the three different settings where trials have been conducted to date (Nepal, Bangladesh, and Pakistan), with a pooled reduction in mortality among those enrolled of 23%. Very early deaths—due primarily to asphyxia—were not included, so the expected reduction in the neonatal mortality rate would be less than this measured 23% effect. Expected impact will vary by setting depending on overall NMR and proportion of deaths actually due to bacterial infection. In high-mortality settings, bacterial infection is generally responsible for a large proportion of newborn deaths, and chlorhexidine could be expected to prevent many of them.

Chlorhexidine can be delivered through existing health services and initiatives such as antenatal, delivery, and postnatal care in the first days and week of life including essential newborn care. It can also be provided through retail outlets including pharmacies, providers working in public facilities and/or communities (e.g., traditional birth attendants), and community health workers who have contact with pregnant women.

Independent operational research in Bangladesh, Nepal, and Pakistan has demonstrated that different formulations (e.g., liquid in a nozzle bottle, gel) of chlorhexidine were acceptable to families and that
families typically were able to use the product as recommended. A pilot study in four districts in Nepal showed that chlorhexidine cord cleansing could feasibly be delivered through the government’s existing cadre of community health workers and female community health volunteers at relatively high coverage.

Based on these findings, the Government of Nepal is now scaling up the use of chlorhexidine for umbilical cord care nationally.

In late 2011, the Government of Nepal approved the use of 7.1% chlorhexidine digluconate for umbilical cord care as part of essential newborn care for both home and facility births. The government has included 7.1% chlorhexidine digluconate on the national essential drug list, with the product provided by a local pharmaceutical company. The government has committed to product procurement beginning the coming fiscal year. Scale-up involves the integration of chlorhexidine into ongoing government services and programs. Chlorhexidine use is being incorporated into pre-service and in-service training curricula for skilled birth attendants. It is expected that by the end of 2014 at least 63 of Nepal’s 75 districts will have been reached.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnosis, treatment or monitoring facilities and skills).

There is a common misconception that the current WHO guidelines advocate for the exclusive use of dry cord care. In fact, in the 1999 WHO document entitled “Care of the Umbilical Cord: A Review of the Evidence” WHO recommends that topical antimicrobials be used on the stump after cutting in home deliveries “…as a temporary measure, according to a local situation (e.g., in neonatal tetanus-endemic areas or to replace a harmful traditional substance).” Additionally, WHO recommends that in institutional deliveries, antimicrobials may be used “according to local situation” and specifically identifies chlorhexidine as one of five recommended antimicrobial agents.

In September 2012, WHO held a consultation meeting to review aspects of postnatal care. The consultative meeting participants reviewed the evidence on chlorhexidine for cord care and made the following recommendation to WHO: Daily application of 7.1% chlorhexidine digluconate to the umbilical cord stump immediately and during the first week of life is recommended for newborns who are born at home in settings with high NMR greater than 30 per 1000. WHO will issue formal guidance within the next four to six months.

10. Summary of comparative effectiveness in a variety of clinical settings.

The September 2012 WHO consultation meeting that reviewed aspects of postnatal care included review of evidence related to chlorhexidine for umbilical cord care. This confidential information includes Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tables that assess the comparative effectiveness of the chlorhexidine product in home birth settings. These data will be published by WHO when they release the results for their review and any new guidance. Because this WHO EMLc application will be posted electronically, the GRADE tables have not been attached to this application so as not to compromise their pending publication by WHO. The GRADE tables will address the identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data) and provide a summary of available data (appraisal of quality, outcome measures, summary of results).
11. **Summary of comparative evidence on safety.**

Chlorhexidine is an antiseptic with a broad spectrum of activity against gram-negative and gram-positive bacteria. There is a 40-year history of chlorhexidine use for the umbilical cord from developed countries as well as widespread experience using chlorhexidine as a presurgical and an oral antiseptic. The safety record has been well established in adults as well as in newborns. For umbilical cleansing, a concentration of 7.1% chlorhexidine digluconate was selected to be sufficiently potent as an antiseptic.\(^{16}\) Overall, chlorhexidine is very safe.

*Estimate of total patient exposure to date*

Chlorhexidine digluconate is a widely used, low-cost antiseptic effective against major agents of neonatal infection. Since its introduction in the 1950s, it has been used regularly as a surgical and detail antiseptic and carefully studied for safety and efficacy. In recent years, tens of thousands of neonates have received a range of chlorhexidine-based cleansing interventions, including full-body and umbilical cord cleansing, without reported adverse effects.\(^{17}\) There are no reports of adverse health consequences as a result of absorption of chlorhexidine in neonates, and there are no data to suggest that the levels of absorption reported have any clinical importance. As noted below, transient contact dermatitis has been reported in preterm very-low-birth-weight infants after long-term (>7 days) placement of chlorhexidine-impregnated dressings for central venous catheters and thus this type of application in these infants should be monitored carefully. In recent community-level RCTs in Nepal, Pakistan, and Bangladesh, data from over 54,000 newborns showed an aggregate 23% reduction in neonatal mortality (not including deaths in the first few hours of life) and a 68% reduction in severe infections for the chlorhexidine intervention groups.

*Description of adverse effects/reactions*

Actions taken to keep the umbilical cord clean will, in general, delay the time to cord separation. Since chlorhexidine is a powerful broad-spectrum antiseptic with residual action due to its tight binding to the skin, application(s) of chlorhexidine to the cord will substantially reduce exposure of the cord to organisms (i.e., from the hands of caretakers, from the environment, etc.). Thus, separation tends to be delayed slightly among babies receiving chlorhexidine to cleanse the cord relative to those not receiving such applications. While not consistent across all studies, delays have been reported in the literature from both hospital-based and community-based studies. Among the five trials (three complete and two ongoing), four have reported on impact of the chlorhexidine cleansing on cord separation time; three of the four found there was some delay among the chlorhexidine group(s). In Nepal, the mean age at separation was 26 hours later in the chlorhexidine group (5.32 days) than the dry cord care group (4.25 days).\(^{18}\) In rural Bangladesh, the mean age at cord separation for babies receiving single (6.90 days) or multiple (7.49 days) cleansings of the cord with chlorhexidine was increased by 2.1 and 2.5 days, respectively, compared to the dry cord care group (4.78 days).\(^{10}\) Preliminary data from Zambia indicate a similar increase of 3.0 days among babies receiving multiple applications of chlorhexidine.\(^{19}\) In contrast to these results, investigators in Pakistan reported no difference in cord separation time between babies receiving different cord care regimens, including multiple cleansings with chlorhexidine.\(^{11}\)

In Nepal and Bangladesh, separation time was also examined for association with increased infection; no association was found. In fact, when increase separation time arises from topical applications of the cord with chlorhexidine, the likelihood of infection in such babies is decreased. All three of the South Asian trials have reported large and statistically significant reductions in individual and combined signs of omphalitis among the chlorhexidine groups.\(^{9,10,11,18,19,20}\)
In 1998, the US Food and Drug Administration (USFDA) circulated a public health notice of possible serious hypersensitivity reactions to chlorhexidine-impregnated medical devices (see: www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/ucm062306.htm).

In the early 1990s, the USFDA cleared three types of medical devices that incorporate chlorhexidine in the composition of the device: intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh. Specifically, reports of adverse events occurring in neonates are as follow:

- In one US study, 6 of 10 neonates weighing less than 1000 grams showed local hypersensitivity reactions to chlorhexidine digluconate-impregnated patches used to secure central venous catheters.\(^{21}\)
- Severe contact dermatitis in seven neonates with this type of dressing was also reported in another US study.\(^{22}\)
- Bradycardia was reported in a neonate associated with a chlorhexidine spray used on the mother’s breasts.\(^{23}\) Two studies have investigated the effect of the use of chlorhexidine associated with central catheter placement in neonates. In one small pilot study of 48 neonates, colonization rates were similar among groups treated with chlorhexidine digluconate or povidone-iodine antisepsis. Dermatitis did not occur among those neonates treated with chlorhexidine digluconate at either central or peripheral catheter sites although seven neonates had measurable chlorhexidine digluconate concentrations during catheterization.\(^{24}\)
- In a larger study of 705 infants comparing the same outcomes, localized contact dermatitis from the chlorhexidine-impregnated dressing occurred in 15 of 98 exposed neonates weighing \(<=1000\) g.\(^{25}\) These results suggest only limited use of the chlorhexidine-impregnated dressing in low-birth-weight infants who require prolonged central access during the first two weeks of life due to the risk of local contact dermatitis.

The BioPatch product (similar to what was used in the above studies), manufactured by Johnson & Johnson (USA), is an antimicrobial dressing used on wounds with percutaneous medical devices and includes a warning to not use on infants under two months of age; please see: http://www.drugs.com/cons/biopatch-w-chlorhexidine-gluconate.html.

It is important to note however that the BioPatch product uses a 20% chlorhexidine concentration which is much higher than the 7.1% chlorhexidine digluconate product used for umbilical cord care. A report from the Johns Hopkins University School of Medicine on results from a national survey of chlorhexidine use among neonates in neonatal intensive care units\(^{26}\) notes that concern was raised only when chlorhexidine was used with external pressure from dressing (consistent with BioPatch use) or with alcohol-based chlorhexidine products (which is traumatic to preterm skin).

*Identification of variation in safety due to health systems and patient factors*

The three countries where chlorhexidine research has been conducted have many factors in common. Neonatal mortality is a high proportion of under-5 mortality, and reduction has stagnated in the latter half of the first decade of this century. In each, institutional deliveries are increasing, but the majority of births still take place at home. All three countries have well-developed essential newborn care policies and guidelines as well as policies on “clean and dry” umbilical cord care. The national neonatal mortality rates range from moderate to high. Challenges to the health systems are similar including insufficient coverage of existing high-priority interventions. All studies applied 7.1% chlorhexidine digluconate liquid on the day of birth, followed by once daily applications ranging from 7 to 14 days post-birth (with one study arm in the Bangladesh study in which application was limited to the day of birth). The studies were
cluster randomized control trials, so the evidence is high grade. Over 90% of the births included in the studies happened at home.

Summary of comparative safety against comparators

In the 1970s chlorhexidine became popular for neonatal use in the United States and elsewhere as hexachlorophene was discontinued. Bathing of newborns in chlorhexidine-based solutions quickly became routine practice in many clinical settings to reduce the occurrence of staphylococcal outbreaks in nurseries.\(^{16,27,28,29}\) Additionally, WHO has recognized chlorhexidine as a suitable antimicrobial for cord care where necessary and especially to displace harmful cord care practices.\(^{15}\) Beyond the direct antiseptic effect, chlorhexidine cord cleansing may replace common practices such as applying harmful substances to the cord.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

Range of costs of the proposed medicine

The price of chlorhexidine for cord care will vary by country and manufacturer. To procure an interim supply from Lomus, the estimated cost is US$0.23–US$0.45 per unit depending on quantity (plus the cost of shipping and any import taxes) for single-application gel, the form used in the Nepal program. Lomus can also provide the liquid formulation in nozzle bottles.

The indicative introductory catalogue price for a 10-ml bottle of 7.1% chlorhexidine digluconate available through the UNICEF Supply Division will be US$0.33. This price is expected to decrease over time as demand for this product increases.

Comparative cost-effectiveness presented as range of cost per routine outcome (e.g., cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

Preliminary cost-effectiveness estimates from the Bangladesh research site sought to determine the incremental cost-effectiveness of any application of 7.1% chlorhexidine digluconate cleansing of the umbilical cord in newborns as compared to dry cord care. Costs were obtained retrospectively from a program perspective based on a review of financial records and in-depth interviews with program staff involved in the initiation and implementation of project activities. Mortality effectiveness estimates were translated into disability-adjusted life years in keeping with WHO-CHOICE\(^{30}\) and recommendations from Drummond, et al.\(^{31}\) for the optimal presentation of economic evaluation findings. Alternative outcomes, including the cost per month of treatment, cost per clinic event/case prevented, cost per cure, etc. limited the generalizability of findings to other contexts, interventions, and, ultimately, alternative resource usages. As such, these were not generated. It is not feasible to collect estimates of the cost per quality-adjusted life year gained in this low-resource setting where methods for weight valuation are not applicable.

Overall, emerging findings suggest that if chlorhexidine is added onto an existing community-based essential newborn care program, the mean incremental cost per disability-adjusted life years averted is less than US$10.00.\(^{7}\) This estimate falls well within the range of other low-cost, high-priority

\(^{\dagger}\) Costs were derived incrementally on top of the existing platform of maternal and newborn health services from a program perspective and included operational and support costs as well as costs associated with product delivery through village health workers and supervising community health workers. Costs may be higher or lower in non-effectiveness trial settings and/or where an existing platform and infrastructure for community-based maternal and newborn health does not exist.
interventions recommended for adoption in South Asia by the Disease Control Priorities Project (2nd Edition) including childhood immunizations for tuberculosis, diphtheria, polio, and measles ($8.00); HIV/AIDS services voluntary testing and counseling, antiretrovirals to prevent vertical transmission, etc. ($68); surgical services and emergency care ($109); community case management of childhood pneumonia ($146); and maternal and newborn care, inclusive of increased primary care, targeted newborn care, and improved emergency and newborn care ($261).  

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well).

UNICEF sourced 7.1% digluconate solution for cord care from Galentic Pharma (India) Pvt. Ltd. (Mumbai, India) and is in the process of updating its supply catalog. The 7.1% chlorhexidine digluconate product manufactured by Galentic is registered in India for export.

7.1% chlorhexidine digluconate is a new product and 7.1% chlorhexidine digluconate is neither part of treatment guidelines in India nor is it in India’s list of essential medicines. The demand for 7.1% chlorhexidine digluconate so far has been driven by the need for various studies which have been conducted outside India. Established demand in India will incentivize Galentic to register its product in India. Please note that it is not unusual for pharmaceutical products to be registered for export only in countries of origin and this is the case for example for antimalarial medicines manufactured in EU.

Lomus Pharmaceuticals Pvt. Ltd (Kathmandu, Nepal) has registered its 7.1% chlorhexidine digluconate gel with the Department of Drug Administration in Nepal for umbilical cord care and provides the product to the Government of Nepal. Lomus is also ready to export the product to other countries.

The product has no regulatory approval from the USFDA or other stringent regulatory body because it is not intended for use in high-resource settings. Similar to other developed-country regulatory agencies, USFDA does not focus on the registration of products for use in developing countries. The chlorhexidine for umbilical cord care product has been developed to be used in low-resource settings where the burden of disease is high.

In 2011, PATH investigated the regulatory pathway for the chlorhexidine for umbilical cord care product. The report assessed various pathways including USFDA, European Medicines Agency, WHO prequalification, and a country-by-country approach. The results suggested that the European Medicines Agency Article 58 procedure might be promising since clinical trial results are already available, the product is a simple formulation, and regulatory assessment of the manufacture and control of this drug product would be considered to be standard. However, certain factors noted below make this option less than desirable:

- It requires significant resources to complete an Article 58 application and maintain the positive scientific opinion resulting from successful submission. It is questionable whether such cost could be justified when using public funds. Also, it might not make sense (even for for-profit organizations) to make such an investment when revenues are expected to be low.

- The holder of the positive opinion has substantial responsibilities, including post-opinion submission of results from any ongoing and future clinical trials and provision of additional information on the product’s efficacy and safety. Although a nonprofit organization can be an opinion holder, it is questionable whether a nonprofit organization would be willing to assume those substantial responsibilities on an ongoing basis.
Manufacturers would need to ensure manufacture of the product from certified sources of active ingredients if the manufacturers were to pursue Article 58. This might negatively affect pricing of the product.

Registration of the chlorhexidine product on a country-by-country basis would still need to be undertaken.

Considering the above, the better choice appears to be a country-by-country approach to secure registration for the chlorhexidine product. An updated listing on the WHO EMLc will likely facilitate regulatory reviews at the country and/or regional level.

14. **Availability of pharmacopoeial standards.**

- Chlorhexidine Gluconate Solution—chlorhexidine active pharmaceutical ingredient.  
- Chlorhexidine Gluconate Topical Solution—chlorhexidine finished pharmaceutical product.

*From British Pharmacopoeia ([http://www.pharmacopoeia.co.uk/pdf/BP2013_Index.pdf](http://www.pharmacopoeia.co.uk/pdf/BP2013_Index.pdf)):*  
- Chlorhexidine Gluconate Gel—may be used for gel product, after analytical methods validation.  
- Chlorhexidine Gluconate Solution—chlorhexidine API.

- Chlorhexidine Gluconate Solution

In addition, the United States Pharmacopoeia/Promoting the Quality of Medicines in Developing Countries project is developing a 7.1% chlorhexidine digluconate monograph/quality standard for liquid/gel to test formulations for compliance (personal communication with Kennedy Chibwe of USP/PQM; November 28, 2012).

15. **Proposed (new/adapted) text for the WHO Model Formulary.**

7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine for umbilical cord care.
Citations/references


