Country Guidance for Umbilical Cord Care

Implementing the World Health Organization's Revised Recommendations on Cord Care

In 2014, the World Health Organization (WHO) released new guidelines on postnatal care, which includes an updated guideline for umbilical cord care:

"Daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1,000 live births).

Clean, dry cord care is recommended for newborns born in health facilities and at home in low neonatal mortality settings. Use of chlorhexidine in these situations may be considered only to replace the application of a harmful traditional substance, such as cow dung, to the cord stump."

In every country setting, to develop sound and effective services, decision-makers must take into account global recommendations, available epidemiologic evidence, and local reality to determine the most appropriate choices in their particular circumstances.

The Chlorhexidine Working Group (CWG) has developed the following guidance to assist countries that are interested in the introduction and scale-up of 7.1% chlorhexidine digluconate (delivering 4% chlorhexidine) for umbilical cord care. **The CWG offers an interpretation of each element of the revised recommendation as well as other considerations for successful implementation of a chlorhexidine for umbilical cord care program.**

Settings for Use

Home and/or Facility Use

The WHO recommends use only on newborns who are born at home. Their recommendation is based on results from clinical trials to date that were conducted only in the home setting. However, newly released data on facility deliveries in Nepal and Bangladesh demonstrate a statistically significant reduction in mortality among those infants randomized to receive chlorhexidine.[1] These data were not available at the time of the WHO review, and countries should take this new information into consideration when developing a chlorhexidine program. Further, facility conditions and the amount of time spent in a facility before release should be considered when determining where to introduce chlorhexidine.

It is widely known that hygienic conditions for home births are a challenge. There also are data demonstrating that hygienic conditions in hospitals are equally challenging, including hospital nursery outbreaks of highly resistant gram negative bacteria.[2] Furthermore, in many high neonatal mortality settings, mothers and newborns are discharged within hours of birth to return home, where hygiene conditions and practices represent a significant risk for life-threatening infection that is preventable through the use of chlorhexidine. While bacterial exposure at birth is a significant factor in the development of sepsis, exposures in the hours and days that follow also are likely to be harmful. Chlorhexidine has a *significant* residual antiseptic effect that inhibits bacterial growth for 24 to 48 hours after application. Whether the birth occurs at home or in a facility, chlorhexidine application at the time of birth provides continued protection during the critical first two days, when risk is greatest for acquiring sepsis due to bacterial exposure through the cord stump.

Country programs could consider:

- Introducing chlorhexidine in multiple settings (i.e., home and facility).
- Introducing chlorhexidine in home settings only.

Settings with a High Neonatal Mortality Rate (NMR)

The WHO recommends chlorhexidine use in settings with a high NMR—greater than 30 per 1,000. Its recommendation is based on clinical trial data collected to date from settings where the NMR was at least 30 per 1,000 live births.

There have been three completed randomized controlled trials (RCTs) for chlorhexidine with decreased mortality outcomes, and two additional trials are underway. As with any RCT using a mortality outcome, sample sizes must be relatively large in order to confer sufficient statistical power. The trials to date were powered to detect a mortality effect, on the assumption of high baseline mortality rates (>30/1,000).

To detect a mortality effect in settings with a lower baseline mortality risk (<30/1,000) would require proportionately larger sample sizes (with resulting consequences for cost and time required). It is unlikely that additional RCTs in settings with lower mortality risk will be implemented.

Countries with a NMR of less than 30 neonatal deaths per 1,000 live births can still benefit from the use of chlorhexidine for umbilical cord care. Also, NMR can vary regionally within a country. Regional NMR data (if available) can be used to assist countries in determining where to prioritize this intervention.

Based on the country-specific situation, country programs could:

- Determine that the entire population could benefit from this low-cost, life-saving intervention, regardless of NMR.
- Consider a regional approach to introduction depending on availability of regional NMR data.

Single-Day versus Multiple-Day Application

The WHO recommends using chlorhexidine for the first week of life. Data show that application on the first day is the most important. Additional use until the cord falls off also has been shown to be beneficial.

Although the WHO consultation recommended multiple-day application, the question of the possible superiority of multiple-day over single-day is not clearly resolved. The design of the trials to date has primarily tested multiple-day application; thus, that is what we have the most evidence for. However, in the original Nepal study, one-third of those randomized to chlorhexidine had application initiated only *after* the first day of life. This group had mortality risk just as high as the control group. By contrast, those starting *on* the day of birth had one-third lower mortality, thus indicating the importance of starting the intervention early. In the Bangladesh study, a single application applied within the first day showed a reduction in mortality risk, while multiple-day application had lower effectiveness. The difference between multiple-day and control groups was not statistically significant.

In different ways, all three studies point to the importance of beginning application as early as possible. Although applying chlorhexidine on the day of birth is the most important, the trials show that multiple-day application provides additional benefit in preventing visible cord infection, which can lead to death. Based on evidence from the three trials and considering messaging simplicity and cost, the government of Nepal has opted for single-day application. As stated previously, chlorhexidine has a significant residual antiseptic effect for 24 to 48 hours. If applied on the day of birth, much (possibly all) of the protection from life-threatening sepsis is achieved.

7.1% chlorhexidine digluconate is available as a gel or as an aqueous solution (liquid). The global CWG recommends the following product sizes. These sizes account for potential wastage and provide a sufficient quantity for the specified period of application.

SINGLE-DAY APPLICATION		MULTIPLE-DAY APPLICATION	
Gel	**Liquid**	**Gel**	**Liquid**
3 grams	10 milliliters	10 grams	30 milliliters

Country programs could consider:

- The evidence and specific country situation to determine if they want to implement the chlorhexidine intervention with single-day or multiple-day application.

Selection of Dosage Form (Gel or Liquid)

Both aqueous solution (liquid) and gel are equally effective for umbilical cord care.[3] Selection of the dosage form (gel or liquid) will depend on which form is most acceptable to mothers, care givers, skilled providers, and others who are likely to use the product; product availability (e.g., ease of production/import and supply sustainability); and an evaluation of the primary containers* for the selected dosage form. The evaluation of the primary containers is an important safety aspect in order to eliminate confusion with other medicines commonly available in the country and thus prevent improper use.

	LIQUID	GEL
PRIMARY CONTAINERS Important factors must be considered to determine the optimal primary container for your setting. NOTE: Drug regulatory officials should be closely involved in decisions regarding dosage form, including specific requirements in regard to safety warnings that must appear on the primary container, patient leaflet, and secondary packaging**.	• Nozzle/dropper bottles for liquid 7.1% chlorhexidine digluconate provide the best product coverage on the umbilical stump. However, depending upon the country, users may associate the small (single-day) application size nozzle/dropper bottles with newborn eye or ear drops. • Spray bottles work only in the upright position and might make it difficult for users to achieve complete coverage of the cord stump. • Wide-mouth bottles may increase the risk of product contamination and spillage.	• Aluminum tubes are commonly used for semi-solid pharmaceuticals and are appropriate containers for gel 7.1% chlorhexidine digluconate. However, depending upon the country, users may associate the small (single-day) application size tubes with newborn eye ointment. • Sachets could be a lower-cost option. However, depending on the country, sachets might not be commonly used for pharmaceuticals; therefore, manufacturers might not have the right equipment, and users might associate sachets with cosmetics rather than medicines, leading to confusion.
PRODUCT AVAILABILITY	At this time, a pharmaceutical company in Bangladesh, which is Good Manufacturing Practices Compliant, and the United Nations Children's Fund (UNICEF) Supply Division Catalogue offer a liquid product for single-day application. The UNICEF Supply Division plans to include a liquid product for multiple-day application in 2016.	At this time, pharmaceutical companies in Kenya, Nepal, and Nigeria, which are Good Manufacturing Practices compliant, are able to export gel 7.1% chlorhexidine digluconate to other countries. These companies provide chlorhexidine gel in sizes appropriate for both single-day and multiple-day use. The UNICEF Supply Division Catalogue does not list a gel product at this time, but plans to include one in 2016.
IMPLICATION TO LOCAL PRODUCTION	It is relatively easier to find pharmaceutical manufacturers that have existing capabilities and capacity for manufacturing liquid forms of pharmaceuticals rather than gel forms. However, careful consideration must be given to determining whether local production of 7.1% liquid chlorhexidine digluconate is feasible, by considering the Good Manufacturing Practices status of pharmaceutical companies as well as a country's regulatory systems and infrastructure.	Manufacturing of gel pharmaceuticals might not be very common in certain low-resource countries; therefore, local production of gel 7.1% chlorhexidine digluconate is likely to be more difficult to achieve than liquid.

*a primary container is the container that is in direct contact with the drug.[4] In this case, a bottle, tube, or sachet.

**secondary packaging is packaging which will not be in direct contact with the drug.[4] In this case, a box or carton.

When used as directed, the safety record of chlorhexidine has been well established in adults and newborns. As with all medications, care must be taken to ensure that the product is used appropriately. Wash hands before and after use. Chlorhexidine should be kept out of eyes and ears. Remaining chlorhexidine product should be discarded after the end of the specified application period.

It is good practice to consult with the national regulatory authority to ensure that the labeling information, patient information leaflet, and instructions for use are consistent with the requirements of the national regulatory authority. Such instructions should warn users to avoid putting 7.1% chlorhexidine digluconate product in the eyes or ears and to discard any remaining product after the specified period of use. Product packaging and labeling should be designed accordingly. Depending on the context, this may entail use of pictorial messages or icons on the primary packaging (e.g. tube or nozzle bottle) as well as including appropriate wording on instructions accompanying the product. In some settings, it may be appropriate to avoid forms of primary packaging that could easily be mistaken for eye or ear care products.

Currently, these sources are available for 7.1% chlorhexidine digluconate:

Liquid: ACI Limited (Bangladesh), UNICEF Supply Catalogue (product number S1531515)

Gel: Drugfield Pharmaceuticals Ltd. (Nigeria), Lomus Pharmaceuticals Pvt. Ltd. (Nepal), Universal Corporation Ltd. (Kenya)

Expected Impact

The impact will depend on the target population.

The effect of size has varied across the three different settings where RCTs have been conducted (Bangladesh, Nepal, and Pakistan), with a pooled reduction in mortality of 23% among babies who received applications of chlorhexidine to the umbilical cord stump. Because the risk of exposures to the cord and distribution of causes of neonatal deaths vary by community, the impact on overall NMR would likely vary depending on setting and population. For impact, a high proportion of the population needs to receive the intervention, and it must be delivered in a manner that ensures its effectiveness. Achieving high coverage is facilitated by simplicity. The lower the cost, the easier the supply chain management. The simpler the application regimen, the better the conditions for achieving high coverage. Regardless, data indicate that this simple and cost-effective intervention can prevent hundreds of thousands of deaths annually.

Country programs should:

- Know that chlorhexidine is a proven intervention that reduces neonatal mortality and cord infection.
- Not expect a significant mortality reduction benefit from this intervention in countries with low neonatal mortality and where hygiene conditions around birth and the first days of life are reliably good.

Additional Information

The **Chlorhexidine Working Group** is an international collaboration of organizations committed to advancing the use of 7.1% chlorhexidine digluconate for umbilical cord care through advocacy, research, and technical assistance. For more information on introducing chlorhexidine in your country or for more information on this intervention, contact the Chlorhexidine Working Group at chx@healthynewbornnetwork.org or visit the technical resource page at: http://www.healthynewbornnetwork.org/page/chlorhexidine-umbilical-cord-care-resource-page.

1 Imdad A, Mullany LC, Baqui AH, et al. The effect of umbilical cord cleansing with chlorhexidine on omphalitis and neonatal mortality in community settings in developing countries: a meta-analysis. *BMC Public Health.* 2013;13(Suppl 3):S15.

2 Zaidi AKM, Huskins WC, Thaver D, et al. Hospital-acquired neonatal infections in developing countries. *Lancet.* 2005;365(9465): 1175–1188.

3 Hodgins S, Thapa K, Khanal L, et al. Chlorhexidine gel versus aqueous for preventive use on umbilical stump: a randomized noninferiority trial. *Pediatr Infect Dis J*. 2010;29(11):999–1003.

4 U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. May 1999.