Supplementary Country Guidance

7.1% chlorhexidine digluconate for application to the umbilical cord stump of the newborn is one of 13 products prioritized by the UN Commission on Life-Saving Commodities for Women and Children and is now on the World Health Organization (WHO) Model List of Essential Medicines for this indication. As such, it is now being widely considered for adoption by ministries of health. As countries move forward to incorporate chlorhexidine into routine newborn care, ministries have a number of decisions to make. There are at least three sets of considerations that can bear on these decisions:

- What are the global recommendations?
- What does the evidence show?
- What makes sense programmatically in your setting?

In adopting use of chlorhexidine for cord care and developing delivery strategies, those charged with developing appropriate and effective delivery strategies have decisions to make on a range of issues. Several of these issues are touched on in recent guidance[1] from the WHO, which reads as follows:

"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 application of a harmful traditional substance, such as cow dung, to the cord stump."

In the following supplement, several design issues raised in this WHO guidance are addressed, notably the following:

1. Application regimen: single-day versus multiple-day.
2. Product form: gel versus liquid.
3. Who should receive it: chlorhexidine use and place of birth.
4. Who needs it: neonatal mortality rate threshold.

Application regimen: single-day versus multiple-day

Epidemiologic considerations

There are three main randomized controlled trials with mortality as an endpoint that are relevant to the question of duration of use (Nepal, Bangladesh, and Pakistan).[2,3,4] In all three, chlorhexidine was applied in the home (in the Nepal and Bangladesh studies, most but not all deliveries were at home).

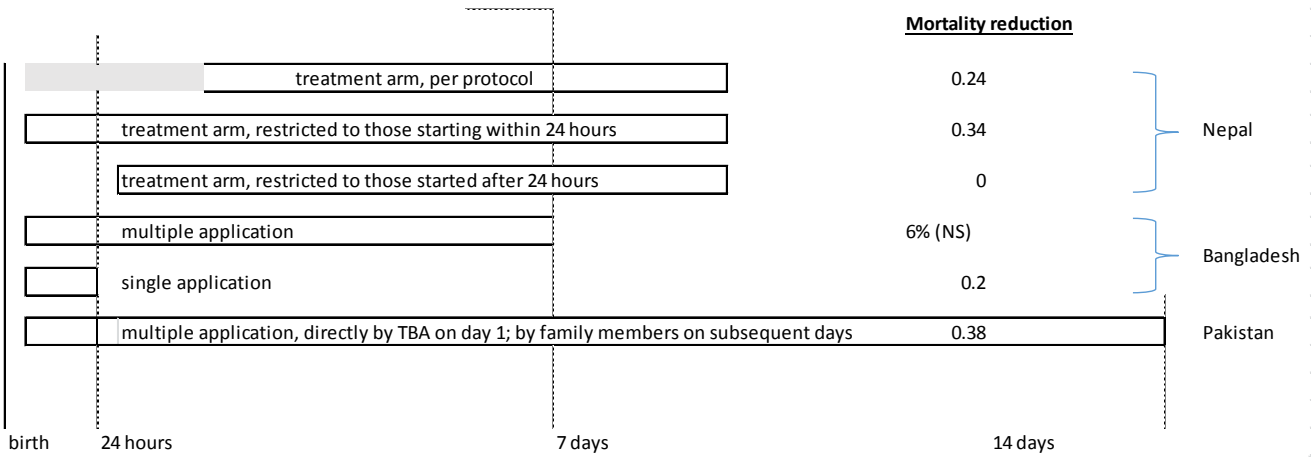
In the first study, conducted in Nepal, participants in the treatment arm were to receive chlorhexidine per the following schedule: days 1–4, 6, 8, and 10.[2] In the Bangladesh study, there were two alternate treatment arms: (a) application on the day of birth only; (b) daily application for a week.[3] In the Pakistan study, the protocol provided for application by a traditional birth attendant (TBA) on the day of birth, then leaving a supply with the family with instructions to continue application daily for 14 days.[4]

In all three studies, efforts were made to ensure that the first application occurred as soon as possible after birth. However, in the Nepal study, more than one-third of those assigned to the treatment arm had the first application more than 24 hours after birth. Analysis of that study showed an overall effect size of 24%. However, in secondary analysis, those randomized to receive chlorhexidine who had the first application *beyond* 24 hours did no better than the controls. Among those who actually had the first application on the day of birth, mortality was 34% lower than among the controls.

In the Bangladesh study, mortality was 20% lower in the single-day application only group than in the controls. Mortality in the multiple-day group, however, was only 6% lower than in the controls, and this difference was not statistically significant. Nevertheless, compared with the controls, likelihood of severe local infection of the cord stump was lower in the multiple-day application group (RR = 0.35) than in the single-day group (RR = 0.77, not statistically significant).

In the Pakistan study, all of those randomized to treatment received the first application of chlorhexidine on the day of birth (applied by the TBA). Family members were advised to continue application daily, on subsequent days. The measured effect size on mortality in this setting was 38% (see Figure 1).

Figure 1: Summary of Pakistan study



At baseline, application of other substances to the cord stump was widespread in the Nepal and Pakistan study sites and somewhat less common in the Bangladesh site. In the Nepal study, approximately half the study subjects in both the treatment and control groups applied other substances to the cord stump, mainly mustard seed oil.

To reduce mortality risk, application needs to be done *on the day of birth*.

Application *beyond day 1* reduces risk of local infection to the cord stump and may further reduce mortality risk.

Programmatic considerations

In some countries considering adoption of chlorhexidine for cord care, there has been concern that this will require significant changes to current cord care *messaging*, which has encouraged dry cord care (keeping the cord clean and dry and not applying anything to it). Largely because of this concern, the government of Nepal (which was the first to adopt and scale up use) opted for day-of-birth application only; this has allowed them to maintain the same clean, dry cord care messaging (beyond immediate care at birth). In some settings, it may be important to have something to offer for continuing use beyond the immediate care at birth.

For *impact*, a high proportion of the population needs to receive the intervention, delivered in a way that ensures its effectiveness. If applied on the day of birth, much (possibly all) of the protection from life-threatening sepsis is achieved, even when other substances are applied on subsequent days. So single-day application can be considered effective, though multiple-day application carries additional benefit.

Achieving high coverage is facilitated by simplicity. The lower the cost, the easier the supply chain management; and the simpler the application regimen, the more favorable the conditions will be for achieving high coverage. These considerations tend to favor either a single application or a size and type of packaging sufficient for multiple-day application but that minimizes additional weight or size (e.g., a tube of 10 grams rather than the 3 grams required for single use).

Production form: gel versus liquid

	LIQUID	GEL
ACCEPTABILITY	The optimal dosage form (gel or liquid) and product presentation (e.g., packaging) may vary depending on the geographical area, user characteristics, and distribution channel (public sector, social marketing, pharmacy retailers, clean delivery kits, etc.). Formative research should be performed to validate which product form and presentation are most preferred by the target population.	
PRIMARY CONTAINERS	• Nozzle/dropper bottles are the optimal primary container for liquid 7.1% chlorhexidine digluconate. • Spray bottles should be avoided since they work only in the upright position and might make it difficult for users to achieve complete coverage of the cord stump. • Wide-mouth bottles also should be avoided due to risk of contamination.	• Aluminum tubes are commonly used for semi-solid pharmaceuticals and are appropriate containers for gel 7.1% chlorhexidine digluconate. • 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, is able to export liquid 7.1% chlorhexidine digluconate to other countries. In addition, the United Nations Children's Fund (UNICEF) Supply Division Catalogue lists 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 Nepal, Nigeria, and Kenya, 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 is not very common in low-resource settings; therefore, local production of gel 7.1% chlorhexidine digluconate is likely to be more difficult to achieve than liquid.

Who should receive it: chlorhexidine use and place of birth

Epidemiologic considerations

At least four papers[2,3,5,6] that report on three different randomized controlled trials with mortality as an endpoint are relevant to the question of use for institutional deliveries (and several other studies use cord colonization by potentially pathogenic bacteria as an endpoint). Only two of these papers were available for consideration at the time of the September 2012 WHO consultation on which the current recommendations are based—the Nepal[2] and Bangladesh[3] studies—neither of which was restricted to home deliveries. They were population-based cluster-randomized controlled trials, in which the majority of births were at home, but in which a big enough subsample was born in health facilities; pooling the results of the two studies, there was adequate significance to detect a mortality effect. Such analysis was not reported in the initial papers available to the reviewers participating in the WHO consultation but is now available in the published literature.[5] This pooled analysis of institutional deliveries in the Nepal and Bangladesh studies shows a statistically significant difference, with 50% lower mortality among those randomized to receive chlorhexidine. Note that because this was a cluster-randomized (rather than individually randomized) trial, such a disaggregated analysis does not break the randomization.

In early 2013 (i.e., after the WHO consultation that was the basis for the recent WHO guidance document), Gathwala published a paper reporting results of a randomized controlled trial of a lower dose of chlorhexidine, administered three times daily to newborn neonatal intensive care unit patients born in a tertiary-care health facility.[6] This study showed a statistically significant benefit both for culture-proven sepsis and all-cause mortality.

Based on evidence now available, there are no sound epidemiologic grounds for restricting use to babies born at home.

Programmatic considerations

Good infection prevention depends on rigorous hygiene practices (e.g., provider handwashing) and liberal use of antiseptics and sterilization. An important principle is to have multiple lines of defense. Even health facilities with good standards for hygiene practices do not rely exclusively on adherence to these behaviors, but also use antiseptics for many purposes.

Although bacterial exposure immediately at birth may be significant in the development of sepsis preventable through the use of chlorhexidine, exposure in the hours and days that follow also is likely to be harmful. In many high-mortality settings, mothers and newborns are discharged within hours after birth, returning home, where hygiene conditions and practices may represent a significant risk for life-threatening infection, preventable through chlorhexidine use. Note that an important benefit of chlorhexidine used in the concentration recommended for cord care is that it has significant residual effect, inhibiting bacterial growth for 24–48 hours after application.[7] Therefore, even for very early hospital discharge, application at the time of birth provides continued protection to the baby at home during the critical first two days, when the risk of sepsis arising from bacterial exposure through the cord stump is greatest.

Another important consideration is that health workers who do not use chlorhexidine themselves are unlikely to be convincing promoters of chlorhexidine for home births. Excluding facility use (which necessarily calls into question the credibility of the intervention) is likely to undermine coverage for home births as well as deprive those born in health facilities of the potential benefits.

Who needs it: neonatal mortality rate threshold

Epidemiologic considerations

Three large, recent, published studies of chlorhexidine for cord care were conducted in settings where the baseline neonatal mortality was greater than 30 deaths per 1,000 live births.[2,3,4] All three studies were conducted in relatively disadvantaged areas within their respective countries and had higher mortality than average for their countries. However, the settings differed in certain significant respects.

In the Pakistan study (which showed the largest effect size), application of non-study substances to the cord was virtually universal, despite counseling to the contrary.[4] In Bangladesh (with the smallest effect size), application of such substances was quite uncommon (6% at the time of delivery, 3% later on).[3] The Nepal study was intermediate in both respects, with about half of newborns having non-study substances applied.[2] In all three sites, application of non-study substances was equally common across treatment and control groups. Of course, application of various substances to the cord is only one means of exposure to potential pathogens. Hygiene conditions in the location where the delivery takes place (and where care is provided at home) and hygiene practices of those handling the newborn also would be expected to contribute to exposure risk.

From the three trials, we have learned that, at least in settings similar to those where the trials were conducted, a large proportion of cases of life-threatening sepsis arise from exposure through the freshly cut umbilical cord stump. Daily *soap and water cleansing* and *counseling on handwashing practices* were tested in the Nepal and Pakistan studies, respectively. Neither reduced mortality risk. But there was a relatively large protective effect from chlorhexidine use. The effect size varied across the three sites, but it is impossible to determine to what extent this reflects statistical noise versus real differences between settings. From each of the studies, results suggest that the protective effect resulted primarily (possibly entirely) from application on the day of birth, when there is still a fresh wound and somewhat patent umbilical vessels. In these settings, a comparatively large proportion of newborns were of low birth weight (30% or more weighing less than 2,500 grams), and 20% or more were born at less than 37 weeks' gestation; host resistance can therefore be expected to contribute to sepsis risk. However, hygiene conditions and practices (including applying substances to the cord) were apparently the most potent contributors to risk of sepsis. The mortality rate, per se, would have no bearing on risk or on efficacy of the intervention. In this particular case, benefit is expected to the extent that there is a risk of sepsis arising from exposure through the cord stump wound. In settings where sepsis arising from this exposure is uncommon, regardless of neonatal mortality rate, one would not expect a significant reduction in risk.

The study results available provide no sound epidemiologic grounds to infer that there is any specific mortality rate threshold below which chlorhexidine would not be expected to confer benefit.

Programmatic considerations

Most countries with high neonatal mortality rely on periodic population surveys (notably, Demographic and Health Surveys) for estimates of neonatal mortality rates. The estimates normally cover a five-year time interval. The sample size determines the degree of precision of the point estimates, but typically the 95% confidence intervals are at least +/-10% from the point estimate, so—for example—a point estimate of 30/1,000 would have a confidence interval extending from about 27/1,000 to 33/1,000 or wider. Some country surveys use quite large samples that have tighter confidence intervals at the national level. These surveys allow generation of subnational point estimates for mortality over the preceding five years, with confidence intervals similar to those of other nationwide Demographic and Health Surveys. In most cases,

however, if subnational estimates are available from such surveys, they are for ten-year time intervals. Generally, obtaining subnational mortality estimates of any useful precision for time intervals that can serve as reasonable proxies for current mortality is not feasible.

Even if it were possible to obtain reasonably accurate and timely subnational mortality estimates, attempting to introduce a program or intervention on a haphazard basis, with some states or districts included and others excluded (or covering only times of the year when neonatal mortality rate can be expected to exceed a certain threshold), would significantly complicate implementation and likely undermine program effectiveness. Practically speaking, governments will generally need to make a decision: *all in* or *all out*.

In settings with a much lower neonatal mortality rate, and where sepsis has been documented to account for a comparatively smaller fraction of newborn deaths, other interventions will likely be prioritized over chlorhexidine.

Program design choices

Epidemiology varies by setting, as do current cord care practices and availability of different types of service delivery channels (e.g., antenatal care, social marketing, presence and role of community health workers). Likewise, local production capacity and costs, and strength of supply chain management, also vary by setting.

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

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[1] World Health Organization (WHO). *WHO Recommendations on Postnatal Care of the Mother and Newborn*. Geneva: WHO; 2013.

[2] Mullany LC, Darmstadt GL, Khatry SK, et al. Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster randomised trial. *Lancet*. 2006;367(9514):910–918.

[3] Arifeen SE, Mullany LC, Shah R, et al. The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster-randomised trial. *Lancet*. 2012;379(9820):1022–1028.

[4] Soofi S, Cousens S, Imdad A, et al. Topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, cluster-randomised trial. *Lancet*. 2012;379(9820):1029–1036.

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[6] Gathwala G, Sharma D, Bhakhri B. Effect of topical application of chlorhexidine for umbilical cord care in comparison with conventional dry cord care on the risk of neonatal sepsis: a randomized controlled trial. *J Trop Pediatr.* 2013;59(3):209–213.

[7] 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.