

CASE STUDY

Chlorhexidine for Umbilical Cord Care



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Acronyms

ASHA	Accredited social health activist
CDK	Clean delivery kit
CHX	Chlorhexidine
EMA	European Medicines Agency
EMLc	Pediatric essential medicines list or model list of essential medicines for children
FCHV	Female Community Health Volunteer
HDPE	High-density polyethylene
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
RCT	Randomized controlled trial
RH	Relative humidity
TBA	Traditional birth attendant
USFDA	United States Food and Drug Administration
WHO	World Health Organization
WTP	Willingness to pay

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Executive Summary

Globally, neonatal infections are estimated to account for over 1 million newborn deaths annually (over a third of the total burden). In many regions, infection is the leading cause of neonatal mortality, and in high-mortality regions infections are responsible for around half of all newborn deaths. Many of these infections come from contamination of the umbilical cord stump.

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. Recent community-level randomized controlled trials in Nepal, Pakistan, and Bangladesh have shown that applying a 4% chlorhexidine product (7.1% chlorhexidine digluconate) to the umbilical cord saves lives (the Pakistan and Bangladesh findings were published in *The Lancet* on February 8, 2012). Across the three countries, 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. These are some of the largest effect sizes seen in any neonatal intervention.

There are literally dozens of manufacturers currently making chlorhexidine-based products around the world, at concentrations from <1% to 20%. Chlorhexidine digluconate—used to make a variety of chlorhexidine finished products—is readily available on every inhabited continent at low cost. The finished product for care of the umbilical cord stump (4% free chlorhexidine, or 7.1% chlorhexidine digluconate) can cost less than US\$0.01 in raw materials per baby. It has a long shelf life, requires no cold chain, and is extremely easy to apply with minimal training and no equipment. These factors make it suitable for hospital, health center, and home care alike. Few other interventions have demonstrated such potential for rapidly reducing newborn mortality across so many settings for such a low cost.

While there have been efforts to improve umbilical cord hygiene by advocating “dry cord care,” these efforts have not always had the intended effect in all settings. Millions of mothers around the world continue to have a strong desire to apply something to the umbilical cord stump of their newborns. In the absence of a specifically recommended product, they resort to a variety of traditional and non-traditional substances including edible oils, ash, dirt, and feces. Where consumer research has been conducted, mothers have shown a strong latent demand for a purpose-made antiseptic like chlorhexidine and also have demonstrated the ability to use chlorhexidine correctly.

Nepal is the first country to have registered a chlorhexidine product specifically for umbilical cord stump care. Additionally, Nepal has included chlorhexidine in their 2011 national list of essential medicines. One of the largest pharmaceutical producers in the country manufactures it for newborn care programs. The government of Nepal has plans to allocate funds in the coming year for procuring the product for broader use.

Several actions are required to take advantage of this opportunity, beyond Nepal, and to address one of the leading causes of neonatal mortality:

- Add 4% chlorhexidine (7.1% chlorhexidine digluconate) for umbilical cord care to the WHO model list of essential medicines for children.
- Correct the common misconception that WHO advocates dry cord care only. The WHO umbilical cord care guidelines recommend that antimicrobials be used “...as a temporary measure, according to a local situation (e.g., in neonatal tetanus-endemic areas or to replace a harmful traditional substance).” These exceptions are rarely cited in discussions of WHO’s dry cord care recommendation but may apply to more than half of all births around the world.
- Fast track registration of 4% chlorhexidine (7.1% chlorhexidine digluconate) for umbilical cord care with national regulatory authorities and encourage additional manufacturers to produce the drug with guaranteed minimum volumes.
- Train birth attendants to correctly apply chlorhexidine to the umbilical cord, as part of newborn care training programs.
- Allocate resources to integrate chlorhexidine for umbilical cord care into essential newborn care programs in order to generate sustainable demand and attractive manufacturing volumes for the product.

Through these actions, we are much more likely to see increased use of this overlooked intervention, thereby contributing to hundreds of thousands of newborns lives saved annually.

1. Efficacy and Effectiveness of Chlorhexidine

1.1. Historical use of the product and safety record

Chlorhexidine (digluconate or gluconate)¹ is a broad-spectrum antiseptic, effective against major agents of neonatal sepsis. Since its development in 1950, chlorhexidine (CHX) has been widely used in a range of applications including hand washes, preoperative body shower, wound care, cosmetics, oral hygiene, general disinfection, and veterinary care. Common formulations can be water-based, alcohol-based, gels, or powders and are commonly applied to adult, infant, and neonatal skin.

Considering the extent of its use as a topical antiseptic on humans, reported side effects are rare, but have included delayed reactions such as contact dermatitis and photosensitivity. Today, topical solutions at the lower concentration of 0.5% chlorhexidine (4% chlorhexidine digluconate mixed with other substances such as isopropyl alcohol) are commonly used for wound care and are widely available over the counter in the United States and in other countries under multiple branded and generic labels.

In the 1970s CHX became popular for neonatal use in the United States and elsewhere as hexachlorophene was discontinued. Bathing of newborns in CHX-based solutions quickly became routine practice in many clinical settings to reduce the occurrence of staphylococcal outbreaks in nurseries.^{2,3,4,5} Additionally, the World Health Organization (WHO) has recognized CHX as a suitable antimicrobial for cord care where necessary and especially to displace harmful cord care practices.⁶

In recent years, tens of thousands of neonates have received a range of CHX-based cleansing interventions, including full-body and umbilical cord cleansing, without reported adverse effects.⁷ There are no reports of adverse health consequences as a result of absorption of CHX in neonates, and there is no data to suggest that the levels of absorption reported have any clinical importance. 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

¹NOTE: It is common practice to use “chlorhexidine gluconate” and “chlorhexidine digluconate” interchangeably when referring to the concentrated chemical antiseptic. “Chlorhexidine digluconate: is used throughout this document for precision and consistency.

² Mullany LC, Darmstadt GL, Tielsch JM. Safety and impact of chlorhexidine antiseptics interventions for improving neonatal health in developing countries. *Pediatric Infectious Disease Journal*. 2006;25:665–675.

³ Maloney MH. Chlorhexidine: a hexachlorophane substitute in the nursery. *Nursing Times*. 1975;71(37):21.

⁴ Rosenberg A, Alatary SD, Peterson AF. Safety and efficacy of the antiseptic chlorhexidine gluconate. *Surgery, Gynecology, & Obstetrics*. 1976;143(5):789–792.

⁵ Tuke W. Hibiscrub in the control of staphylococcal infection in neonates. *Nursing Times*. 1975;71(37):20.

⁶ World Health Organization. *Care of the Umbilical Cord: A Review of the Evidence*. Geneva: WHO/RHT/MSM; 1999. Available at: <https://apps.who.int/rht/documents/MSM98-4/MSM-98-4.htm>.

⁷ Mullany LC, Khatri SK, Sherchand JB, et al. Bacterial colonization of hospital-born infants in Nepal and impact of chlorhexidine skin cleansing: a randomized controlled trial. *Pediatric Infectious Disease Journal*. 2008;27(6):505–511.

thus this type of application in these infants should be monitored carefully. Overall, CHX is very safe.⁸

1.2. Completed studies for umbilical cord care

In 2004, a Cochrane review concluded that there was insufficient evidence to recommend topical antiseptics for prevention of umbilical cord infection (RR=0.53 [0.25–1.13]).⁹ Of the 21 studies included in the most recent version of the review, all but one took place in developed countries (one was in a Bangkok tertiary care teaching hospital). In such environments, only seven studies reported cord infection, and the overall rate of infection was low. CHX was only used in one study. No deaths were reported in any of the studies. This combination of factors limits the extent to which that Cochrane review can inform decision-making about optimal cord care practices in the developing world contexts where neonatal infection is highest.

In recent years, three large community-based randomized controlled trials (RCT) evaluating the effectiveness of CHX for umbilical cord care as part of a package of newborn interventions have been conducted in Nepal, Pakistan, and Bangladesh. A simplified summary of each study is provided in Table 1 below.

Table 1. Clinical trials evaluating the effectiveness of chlorhexidine for umbilical cord care.

Study Characteristic	Nepal	Bangladesh	Pakistan
Overall NMR* (at time of study)	30/1000	36/1000	30/1000
Percent of Births at Home (at time of study)	92%	88%	80%
Total Sample Size	15,123	29,760	9,741
Primary Outcomes	Neonatal mortality Omphalitis	Neonatal mortality Omphalitis	Neonatal mortality Omphalitis
Comparison Group	Dry cord care	Dry cord care	Dry cord care
Frequency of Multiple Applications (day)	1,2,3,4,6,8,10	1,2,3,4,5,6,7	Daily for 14 days
Intervention Provider	Project staff	Project staff	TBA [†] and caretaker

*Neonatal mortality rate.

[†]Traditional birth attendant.

The full details of the Nepal study were published in *The Lancet* in 2006¹⁰ while results of the other two trials were published online on February 8, 2012.^{11,12} All three studies showed substantial

⁸ Mullany LC, Darmstadt GL, Tielsch JM. Safety and impact of chlorhexidine antiseptics interventions for improving neonatal health in developing countries. *Pediatric Infectious Disease Journal*. 2006;25:665–675.

⁹ Zupan J, Garner P, Omari AA. Topical umbilical cord care at birth. *Cochrane Database of Systematic Reviews*. 2004;(3):CD001057.

¹⁰ Mullany LC, Darmstadt GL, Khatri SK, et al. Topical applications of chlorhexidine to the umbilical for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomized trial. *The Lancet*. 2006;367:910–918.

¹¹ Soofi S, Cousens S, Imdad A, Bhutto N, Ali N, Bhutta ZA. 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. *The Lancet*. Published online February 8, 2012.

reductions in neonatal mortality (20% to 38%) and even greater reductions in omphalitis (24% to 75%) in the CHX groups. Several groups have conducted meta-analyses using the data as reported, and the unpublished analyses suggest reduction in mortality of approximately 20% to 23%. More formal meta-analyses are due for publication in the coming months.

Additionally, Hodgins et al. published a trial showing the non-inferiority of 4% CHX gel to 4% CHX liquid. The study, based in Kathmandu, recruited 653 neonates in a hospital setting and showed that 24 hours after application, liquid CHX offered a 64% reduction in the proportion of samples positive for bacteria, whereas gel CHX offered an 86% reduction in the proportion of samples positive for bacteria.¹³

Overall, there is currently sufficient evidence to recommend a 4% CHX product (7.1% CHX digluconate) for umbilical cord cleansing as a strategy to reduce neonatal mortality in settings with poor hygiene and high neonatal mortality.

1.3 Additional studies under way on umbilical cord care

Two additional RCTs are under way to determine the effectiveness of CHX in Africa. Both are expected to report results in 2014.

Table 2. Clinical trials currently under way.

	Pemba (Tanzania)	Zambia
Institutional Lead	The Johns Hopkins University	Boston University
Trial Type	Individually randomized, double-blind, placebo-controlled trial	Cluster randomized, unmasked comparison versus “dry” cord care
Sample Size	24,000 + additional 4,000	42,570 (90 clusters)
Product Type	10-mL dropper bottle of liquid 4% CHX (7.1% CHX digluconate)	10-mL dropper bottle of liquid 4% CHX (7.1% CHX digluconate)
Delivery Method	Project staff demonstrate for mothers four times, mothers apply in other cases	Mothers
Intervention Duration	10 days, or three days after the stump separates, whichever is longer	Ten days, or three days after the stump separates, whichever is longer
Outcomes	Primary: mortality. Sub-study will examine impact on omphalitis as well as the etiology, sensitivity, and specificity of diagnosing omphalitis	Primary: mortality, Secondary: Incidence of omphalitis through 28 days

¹² El Arifeen S, 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. *The Lancet*. Published online February 8, 2012.

¹³ Hodgins S, Thapa K, Khanal L, et al. Chlorhexidine lotion vs. aqueous for preventative use on umbilical stump: a randomized non-inferiority trial. *Pediatric Infectious Disease Journal*. 2010;29(11):999–1003.

2. Global Policy and Regulation

2.1 WHO guidelines for umbilical cord care

There is a common misconception that the 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).”¹⁴ Additionally, WHO recommends that in institutional deliveries, antimicrobials may be used “according to local situation” and specifically identifies CHX as one of five recommended antimicrobial agents.

2.2. The World Health Organization Model List of Essential Medicines for Children

The 2011 WHO Model List of Essential Medicines for Children (EMLc)¹⁵ includes CHX 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 trial in Nepal showed a significant reduction in neonatal mortality after use of a 4% CHX solution (7.1% CHX 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% CHX product at that time, this recommendation of the expert review committee resulted in listing 20% CHX (digluconate) with an instruction to dilute for umbilical cord care use. At the time of publication of the 2009 WHO model list, PATH and the US Agency for International Development submitted a joint letter 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% CHX 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.

Clarity on the use of 4% CHX for umbilical cord care is critical because there is a very common confusion around the concentrations of free chlorhexidine versus chlorhexidine digluconate. The conversion between the two is listed in Table 3 below. It is worth noting that the current listing of 5% CHX digluconate would deliver approximately 2.8% free CHX, a level lower than what was used

¹⁴ World Health Organization. *Care of the Umbilical Cord: A Review of the Evidence*. Geneva: WHO/RHT/MSM; 1999. Available at: <https://apps.who.int/rht/documents/MSM98-4/MSM-98-4.htm>. Accessed February 10, 2012.

¹⁵ World Health Organization. *Model List of Essential Medicines for Children*. 3rd list. Geneva: WHO; March 2011. Available at: http://whqlibdoc.who.int/hq/2011/a95054_eng.pdf. Accessed February 10, 2012.

in the RCTs for umbilical cord care. If one is not aware of this difference, one may see 5% CHX on the EMLc and incorrectly think that one does not have to go through any in-country regulatory process because the 5% is higher than the 4% for umbilical cord care.

Table 3. Free chlorhexidine versus chlorhexidine digluconate.

Chlorhexidine Digluconate	Free Chlorhexidine	Notes
20%	11.3%	Concentration listed on the EMLc
7.1%	4.0%	Concentration used in the RCTs in five countries
5%	2.8%	Concentration listed on the EMLc

To avoid this confusion, the EMLc should state:

Chlorhexidine

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

In 2010, PATH submitted an amendment with additional data to the WHO expert review committee to support the clarification of the indication for use of CHX for umbilical cord care by stipulating use of 4% CHX in either gel or aqueous solution. The expert committee decided to maintain the previous listing for CHX until a product of the strength and formulation used in the trials is commercially available (i.e., availability of the product on the open market, not just for trial purposes). Specifically, The Unedited Report of 18th Expert Committee on the Selection and Use of Essential Medicines (21 to 25 March, 2011) 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.”

Today, there is one company, Lomus Pharmaceuticals Pvt. Ltd (Kathmandu, Nepal), producing a 4% CHX product commercially. It has been in use in four districts (and a larger procurement is currently underway), but could be made available for sale anywhere in the country and for export. Lomus has registered the product with the Department of Drugs Administration in Nepal. Additionally, 4% CHX (7.1% CHX digluconate) is on Nepal’s national essential medicines list for 2011 as a solution or gel for umbilical cord care. This data may help to add 4% CHX (7.1% CHX digluconate) to the WHO EMLc.

3. National Regulatory Policy

CHX is included in some national essential medicines lists, but Nepal is the only country known to have added it to their national essential medicines list at a 4% concentration for umbilical cord care. In other countries it is not at the correct concentration for umbilical cord care. Experience in Bangladesh and Nepal to date demonstrates that CHX for umbilical cord care has been classified by country regulatory agencies as a medicine, and the product is required to be registered in country with the appropriate drug authority. Over-the-counter distribution of the product is independent of the need to register the product as a medicine.

In 2011, PATH reviewed various global regulatory pathways for CHX for umbilical cord care. Pathways investigated included United States Food and Drug Administration (USFDA), European Medicines Agency (EMA), WHO prequalification of medicines, and a country-by-country approach. The results of this review suggest that the EMA procedure (termed Article 58) might appear to be promising in certain respects. Article 58 was established in 2004 to facilitate developing-country registration of medicines to prevent or treat diseases of major public health interest.

Per Article 58 requirements, since the CHX product is a simple formulation, regulatory assessment of the manufacture and control of this drug product would be considered to be standard. Results from clinical trials in South Asia are also available; however, certain factors make this option less than desirable:

- Significant resources are required 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 to make such an investment of several hundreds of thousands of dollars 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 increase costs and therefore pricing of the product.
- Registration of the CHX product on a country-by-country basis would still need to be undertaken.

Considering the above, a country-by-country approach would appear to be the better approach to take to secure registration for a CHX product. An expert consultation with WHO should take place after publication of recent RCT results in Bangladesh and Pakistan. Favorable findings from this consultation, along with an updated listing on the EMLc, will likely facilitate regulatory reviews at

the country and/or regional level. Obtaining WHO prequalification could be explored concurrently if this approach is determined to be reasonable considering time and resource requirements.

3.1. South Asian countries: Nepal, India, Bangladesh

Country-level regulatory processes vary from country to country. A country-level registration process should only be undertaken where the CHX product intervention will be rolled out in the same country. This is the case, for example, in Nepal, where the intervention has been recently approved by the Ministry of Health and Population and the product has obtained registration in country. In Bangladesh, for example, registration would be very straightforward to obtain by Popular Pharmaceutical Ltd, the manufacturer of the product used in the most recent study. However, they would need an incentive to do (i.e., assurance of market demand) that could be demonstrated by an enabling policy environment and firm support for the intervention on the part of the Ministry of Health and other key stakeholders. While India may appear to be a good entry point for product registration in the region, product registration is subject to approval by the Drug Controller General of India, and the data requirements for approval are yet to be determined.

3.2. African countries: Zambia, Tanzania, others

Given the status of ongoing RCTs in Zambia and Tanzania, national regulatory authorities will likely be most interested in product registration after the RCTs are completed. If RCT results are favorable, and corollary ministry of health policy and stakeholders are supportive of the intervention, it is possible that that the product could be registered relatively easily. Regulatory approval obtained in one country may be applied to other countries thereby facilitating market clearance in sub-Saharan Africa. Some countries in the region, however, may prefer to have more localized data about the intervention before giving market clearance for the CHX product.

4. Financing Chlorhexidine

4.1 Cost and cost-effectiveness data

Assuming that every baby requires 3 g of a 4% CHX product (as is provided in the Nepal programs), a finished pharmaceutical product costs less than \$0.005 in raw materials and an additional \$0.09-0.15 in packaging costs. Preliminary estimates of cost effectiveness from a cost effectiveness study in Sylhet, Bangladesh, suggest that when umbilical cord cleansing with a 4% CHX product is added to a platform of community-based maternal and newborn health services, the mean incremental cost per disability-adjusted life year (DALY) averted is less than US\$10.00.^{16,17,18}

¹⁶ NOTE: Costs were derived incrementally on top of existing platforms 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.

4.2 Current use in Nepal

CHX for umbilical cord care is currently used in four districts of Nepal (Parsa, Banke, Jumla, and Bajhang). To date, the programs have been donor financed, effectively working as “at scale” demonstrations. Given the strong results in these pilots, the Government of Nepal is in the process of creating a budget to procure CHX from a local manufacturer (Lomus Pharmaceuticals) for distribution primarily via Female Community Health Volunteers (FCHV). Donor funding is likely to support continued procurement for the FCHVs until government funding is available (expected in 2013). The Lomus product is listed with a maximum retail price of 18 Nepali Rupees (approximately US\$0.22) for a single application, but the actual transfer price between Lomus and the Government of Nepal is not known at this time. Additionally, Lomus hopes to sell the product via its traditional retail channels.

4.3 Potential for public procurement

The low cost of CHX—and particularly the low cost per life saved—makes it among the “best buys” in neonatal health and an excellent candidate for public procurement in countries with high mortality due to neonatal infection.

4.4 Potential for private purchase

The majority of health care expenditure in much of the developing world is private expenditure, and the countries where neonates die from infections are no exception. Table 4 below shows private expenditure on health as a percentage of total expenditure on health for selected countries.

¹⁷ NOTE: This estimate falls between childhood immunizations for TB, DPT, polio and measles (\$8.00); and other common programs like HIV/AIDS services voluntary testing and counseling, ARVs 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).

¹⁸ Musgrove P, Fox-Rushby J. Cost-effectiveness analysis for priority setting. In: Jamison D, Breman JG, Measham AR, et al., eds. *Disease Control Priorities in Developing Countries (2nd edition)*. Washington, DC: The World Bank and Oxford University Press; 2006.

Table 4. Private expenditure on health as a percentage of total expenditure on health.

Country	Annual Estimated Neonatal Deaths from Infection**†	% Private Expenditure ‡
India	405,848	68%
Nigeria	150,459	63%
Pakistan	119,122	68%
DR Congo	109,091	46%
Ethiopia	66,159	48%
Bangladesh	45,722	69%
Tanzania	32,037	28%
Zambia	14,461	38%
Nepal	9,004	62%

*Source: Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379:2151–2161.

†Partnership for Maternal, Newborn & Child Health.

‡Source: WHO; 2008.

Private-sector sales are often an important complement to public-sector provision. As a relatively low-cost, easy-to-use product with a long shelf life, CHX may be particularly well suited to private-sector sales. Data on willingness to pay (WTP) specifically for CHX is scarce, but the data in Table 5 provides some indication for South Asia.

Table 5. Willingness to pay in South Asia.

Country	WTP Range in US\$	Type	Source	Year
Nepal	\$0.05–\$0.06	TBA's stated WTP	Tuladhar et al.	2007
Bangladesh	\$0.42–\$0.70	Actual purchases	Winch et al.	2009
Bangladesh	\$0.21–\$0.85	Mothers' stated WTP	ICDDR,B	2010
India (urban)	\$0.50–\$0.70	Mothers' stated WTP	Synovate	2011
India (rural)	\$0.30–\$0.40	Mothers' stated WTP	Synovate	2011

These WTP figures are 50% to 200% greater than the projected wholesale cost of CHX, leaving potential retail margins for private-sector delivery.

5. User-Centered Product Design: What Women Want

Umbilical cord care is a culturally mediated practice wherein consumer preferences are a key driver of what products are ultimately adopted and discarded. In many communities, there is a deep desire to dress the cord with something, but practices vary widely. Thoughtful combination of formulation and packaging may increase the product's adoption in a specific community.

5.1 Formulation considerations

Based on the clinical trials conducted in South Asian countries and a subsequent test to establish non-inferiority of the 4% CHX gel, the product can be formulated into either aqueous solution (liquid) or gel. Table 6 illustrates several efforts to assess user preferences in regions of interest.

Table 6. Efforts to understand user preferences.

Country	Preference	Notes
Bangladesh	Gel	In 2010, PATH and ICDDR,B assessed the demand for the product among potential users (women who were currently pregnant or had a child over the last six months, and their husbands). The study indicated that when shown concept cards depicting a gel formulation and an aqueous solution 63% of the respondents (1,109 people) preferred gel formulation over aqueous solution. However, the price they were willing to pay did not differ significantly between the two formulation concepts.
Nepal	Gel	The randomized non-inferiority trial conducted in Nepal in 2009 included questions regarding user preference of dosage forms. Of the 30 subjects originally given gel (excluding those woman reporting a negative experience), 2 preferred aqueous. However, over half of those using aqueous indicated they would have preferred gel (17/30), believing that it would stay in place more easily and be longer lasting.
India	Gel	In 2011, a consumer research group polled mothers, mothers-in-law, and caregivers in Uttar Pradesh for product preferences using an unlabeled tube of Lomus 4% gel and an unlabeled 70-ml bottle of aqueous. The majority of respondents across all participant groups preferred the gel.
Tanzania	Liquid	The Pemba study looked at consumer preferences for aqueous formulations in 10-ml and 100-ml bottles as well as tubes of gel formulations. 44.6% of mothers preferred the 10-ml bottle, 33.9% preferred the tube of gel, and 21.5% preferred the 100-ml bottle.
Zambia	Liquid	The Zambia study looked at 10-ml and 100-ml liquid presentations as well as tubes that would contain a gel formulation. Unfortunately, the tubes did not contain CHX gel (a major limitation of the study) and were therefore not popular among respondents.

5.2 Packaging considerations

Primary container for liquid. Both the Nepal and Bangladesh trials used a white Boston round bottle as the primary container (a Boston round bottle can be seen in Figure 1 below) and a cotton ball as the applicator. In the operations research conducted in Bangladesh, a white high-density polyethylene (HDPE) bottle with a nozzle was selected as the material for the primary container for the 4% CHX aqueous solution because: 1) HDPE is the most common plastic material for CHX digluconate-based drugs, 2) the color white protects CHX digluconate from sunlight, and 3) the nozzle minimizes occasions in which users directly contact the umbilical cord. The results from the following two studies led to selecting the white HDPE bottle with a nozzle:

- PATH conducted a product attribute study in 2008. This study compared these three options: 1) white HDPE bottle with a nozzle, 2) white Boston round bottle, and 3) amber glass bottle. Results indicated that the white HDPE bottle with a nozzle was the option most preferred by users and service providers (141 out of 165 respondents [or 85.5%] chose this option).
- The pretesting that the Projahnmo study group conducted with health counselors in 2008 indicated that the 4% CHX aqueous solution was properly applied to the umbilical cord with a nozzle bottle and confirmed their decision to select a nozzle bottle as the primary container.

Primary container for gel. In Nepal, a preprinted aluminum tube (a common primary container for semi-solid drug products) was selected for the 4% CHX gel formulation. While other types of primary containers could be applicable for 4% CHX gel including sachets and plastic tubes, consumer research suggested that mothers and caregivers associated this type of packaging with pharmaceutical products and good health.

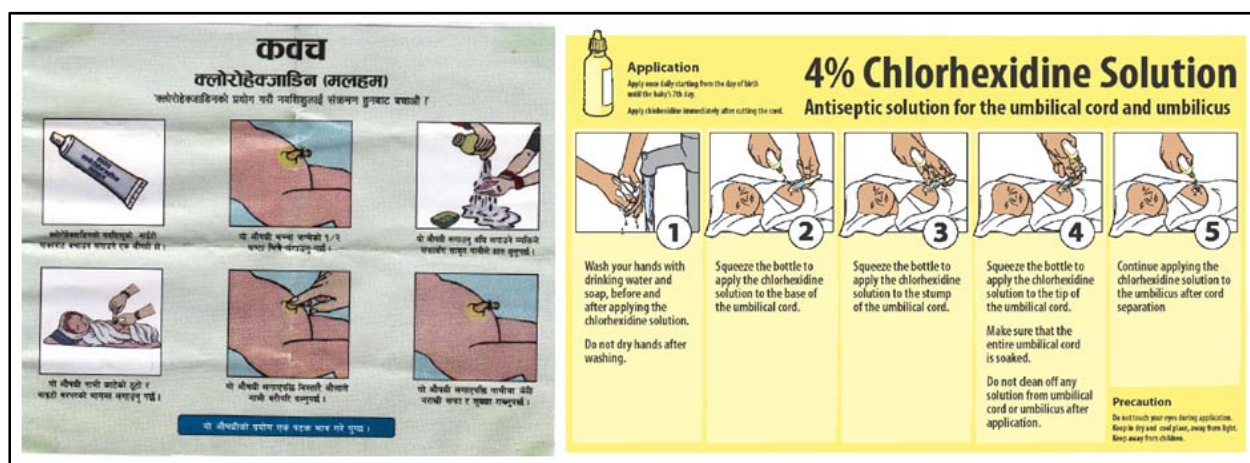
Secondary packaging. The operations research in Bangladesh did not utilize a secondary package. The information required by the drug authority in Bangladesh was printed on a label designed by the manufacturer, which was attached to the primary container. Pictorial instructions for use were developed through collaboration among Projahnmo study group members, PATH, and Popular Pharmaceuticals in order to supplement the instructions-for-use text printed on the label. These supplemental pictorial instructions were then attached to the container with a rubber band. In Nepal, the aluminum tube containing 4% CHX gel was packaged in a small paper box preprinted with labeling information.

Please see Figure 1 below for packaging examples and Figure 2 for examples of instructions for use.

Figure 1. Liquid primary packaging as produced by a manufacturer in Bangladesh for study purposes only (left); primary and secondary packaging of gel product as produced by Lomus in Nepal (right).



Figure 2. Pictorial instructions for use used in Nepal (left) and Bangladesh (right).



5.3 Bundling with clean delivery kits

Some have advocated the bundling of a CHX product with clean delivery kits (CDK) as a way to increase availability and use of the product. To date, such bundling has not occurred. In Nepal, CHX will not be bundled with the clean delivery kit currently being distributed by Contraceptive Sales Company. In Bangladesh, physically bundling a 4% CHX product with a CDK (putting CHX and CDK into the same package) will likely require additional regulatory approval since CHX is a pharmaceutical product and the other contents of the CDK are not. Instead of bundling the two products, nongovernmental organizations that distribute CDKs may use their own depot holders or community workers to present the CHX and CDK concurrently and explain how using both could be beneficial.

6. Manufacturing

6.1 The global chlorhexidine industry

Chlorhexidine digluconate is broadly available around the world both in its bulk drug form of 20% chlorhexidine digluconate and in myriad finished products. In India alone there are over 70 brands of finished CHX products for sale from over 60 different companies. The product has applications as both a preservative and active ingredient across a broad range of veterinary, dental, and other health care applications, as summarized in Table 7.

Table 7. Various uses for chlorhexidine.

Application	Concentration of chlorhexidine digluconate
Veterinary	20%
Mouthwashes, toothpastes, oral rinses	0.12%–0.2%
Skin prep for surgery, procedural hand washing	0.5%–4%
Wound treatment	4%

The drug monograph of 20% chlorhexidine digluconate is listed in United States, United Kingdom, European, and Japanese pharmacopeias. There are also more than 50 vendors of bulk 20% chlorhexidine digluconate concentrate, several of which have Drug Master Files with USFDA. The bulk product is typically sold in 200 kg drums, and there are sufficient buffer stocks on every inhabited continent. Commodity pricing for this product is often in the range of US\$4.50 per kilogram.

Assuming that every baby requires 3 g of a 4% CHX product (as is provided in the Nepal programs), the total requirement of 20% CHX digluconate would be just over 1,000 L per million children treated, or just five drums of active pharmaceutical ingredient per million newborns. Global supply of the active pharmaceutical ingredient, therefore, is unlikely to be a concern.

6.2 The finished product manufacturer's business case

CHX for umbilical cord care is a low-volume, low-margin product with few barriers to entry. If the product is used in all births in a given region, annual sales would correlate with crude birth rates of 30–50 births per thousand in high fertility areas. This is a relatively low sales volume when compared with other pharmaceutical manufacturing opportunities for more commonly used over-the-counter products. Margins for CHX are likely to be similarly lackluster for a product which is in the public domain (not patentable) and quite simple to make. The combination of these factors means that large pharmaceutical companies are unlikely to take an interest in independent manufacture and distribution of CHX for umbilical cord care. Institutional buyers and large volume orders are more likely to attract the attention of potential manufacturers, similar to what took place with Lomus Pharmaceuticals in Nepal.

6.3 Local versus centralized manufacturing of finished products

There are several reasons to consider local manufacturing of a CHX product for umbilical cord care. Capital costs of manufacturing are relatively low, and standard equipment found in most pharmaceutical companies would be used. The manufacturing process is simple and robust enough to be easily replicated. Bulk chlorhexidine digluconate can be purchased in 200-kg drums or even 20-kg pails. Small amounts of the bulk drug yield a large volume of finished CHX product for umbilical cord care. For example, a 20-kg pail of chlorhexidine digluconate can serve about 20,000 newborns at the dose and duration used in Nepal. Local manufacturing can also simplify local regulation where indigenous pharmaceutical companies may be better equipped than foreign firms to navigate an approval process.

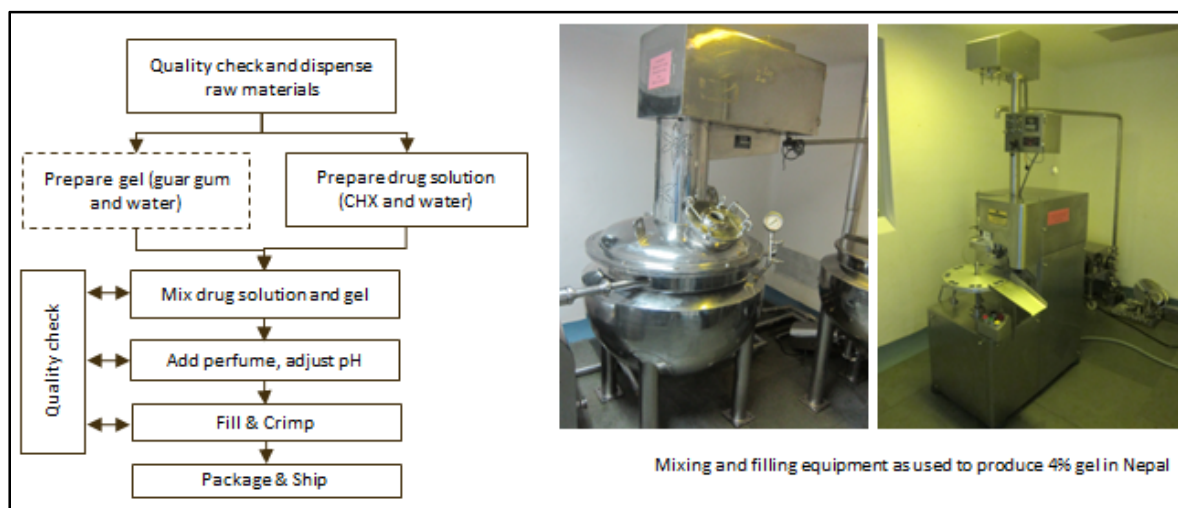
Central manufacturing also has some benefits. A single, central manufacturer may be more compelled by the business case of manufacturing a very high-volume, low-cost product. And should there be a pooled procurement, a centralized manufacturer would also simplify logistics and quality control. The shelf life at 40°C with 75% relative humidity (RH) is sufficient to withstand warehousing and shipping in most climates.

Ultimately, the choice of local versus central manufacturing should be made for business reasons, depending on what type of manufacturer is able to offer the most competitive price on the shortest timeline.

6.4 Formulation details

CHX for umbilical cord care may be formulated as a topical gel or liquid, which have very similar manufacturing processes, as diagrammed below in Figure 3—the only difference being the addition of guar gum (box with dotted lines) to thicken the product into a gel if desired.

Figure 3. Potential manufacturing processes.



Some manufacturers have chosen to add small amounts of benzalkonium chloride to CHX products as a preservative, but stability tests conducted by PATH have shown that this may not be a crucial addition. Additionally, some manufacturers have added perfume and coloring as per consumer preferences.

Over all, the inputs for CHX manufacturing are inexpensive. One representative formulation for gel is detailed below in Table 8.

Table 8. A representative formulation for chlorhexidine gel.

Formula Component	Formulation	Cost in US\$ per 3 g	Source
20% CHX gluconate/digluconate, BP*	7.10%	\$0.004795	Viporchemicals.com
50% benzalkonium chloride (optional)	0.10%	\$0.000000	Alibaba.com
Guar gum, NF [†]	1%	\$0.000060	Alibaba.com
Sodium hydroxide, NF	pH to 6.0	\$0.000009	Alibaba.com
Purified water, USP [‡]	Remainder	\$0.000001	(estimated water tariffs)
Total		\$0.004865	

*British Pharmacopoeia.

[†]National formulary.

[‡]United States Pharmacopoeia.

6.5 Packaging details

Packaging is responsible for most of a CHX product’s cost. For liquid formulations, bottles or sachets may be used. Dropper bottles have been used in all of the RCTs to date and typically cost around US\$0.15 each including filling. Sachets may pack more tightly and ship more easily and often have packing and filling costs in the range of US\$0.01 in India.

The only CHX product packaged for retail sales is made by Lomus Pharmaceuticals in Kathmandu. Based on user feedback, their packaging includes a tube for the gel, a full color instructional package insert, and an outer box (please refer to Figures 1 and 2 above), totaling approximately US\$0.09 (Table 9).

Table 9. Packaging costs example.

Packaging Component	US\$ per Unit	Source
Preprinted collapsible aluminum tube	\$0.04	Perfect Tubes Pvt
Printed paperboard box	\$0.04	Lomus Pharmaceuticals
Printed color package insert	<\$0.01	Lomus Pharmaceuticals
Total	\$0.09	

7. Supply Chain Management

7.1 Shipping considerations

Temperature, pH level, and exposure to sunlight adversely affect the stability of CHX digluconate, the active ingredient of 4% CHX for umbilical cord care. When CHX digluconate is kept under suboptimal conditions, it degrades to p-chloroaniline and its purity is compromised. According to the US Pharmacopeia, a 20% aqueous solution of CHX digluconate should maintain its pH range between 5.5 and 7.0. It also states that 20% CHX digluconate should be preserved in a tight container at room temperature and be protected from light. These requirements should also be maintained for shipping and storing 4% CHX for umbilical cord care.

In addition, selecting an appropriate primary container is important in order not only to maintain the quality of the product but to minimize its shipping cost. The quality of the CHX digluconate would be best preserved with neutral glass or polypropylene. Also, transparent primary containers should be avoided in order to protect CHX digluconate from light. A commonly used primary container for commercially available CHX digluconate-based products is HDPE since it is lighter than glass (thus reduces shipping cost) and it maintains product quality. As an example, Medichem S.A. (Barcelona, Spain), one of the 20% CHX digluconate manufacturers listed in the Drug Master File submitted to the USFDA, provides its product in a 200-kg HDPE drum. In any case, manufacturers should perform compatibility tests according to local regulations in order to confirm the appropriateness of the selected primary containers.

7.2 Shelf life

A drug product's shelf life is the length of time during which it is considered suitable for sale, use, or consumption. Shelf life is affected by temperature, humidity, and light. For this reason, according to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), each country is classified into one of four climatic zones with defined storage conditions for drug substances and products (see table below). Based on this classification, in South Asia, Bangladesh and India are both assigned to Zone IV, whereas Nepal is assigned to Zone II. In Africa, Tanzania is assigned to Zone IV whereas Zambia is assigned to Zone II.

Table 10. Climatic zones for shelf life.

Climatic Zone	Definition	Storage Condition
I	Temperate climate	21°C/45% RH
II	Subtropical and Mediterranean climates	25°C/60% RH
III	Hot, dry climate	30°C/35% RH
IV	Hot, humid climate	30°C/70% RH

Source: ICH Q1F Guideline, "Stability Data Package for Registration in Climatic Zones III and IV."

Manufacturers of 4% CHX products must perform stability tests using the primary container that they selected for their products in order to establish their product shelf life under the storage conditions assigned to the country in which the products will be distributed and used. Stability tests can be performed using accelerated conditions (e.g., in general, 40°C ± 2°C/75% RH ± 5% RH for 6 months for climatic zones III and IV). In addition to this ICH guideline, manufacturers need to check with their local drug regulatory authority to ascertain whether there are any additional requirements.

In 2009, PATH commissioned a contract laboratory in the United States to perform stability tests on the 4% CHX aqueous solution and gel. Testing was conducted under the following protocol:

- Primary container: 4-mL HDPE bottle and polypropylene screw closure (materials commonly used for commercial CHX-based products).
- Testing conditions: 5°C, 25°C/60% RH and 40°C/75% RH to establish 24-month stability.
- Tested at: 0, 1, 3, and 6 months.
- Tested for: appearance, pH, potency, and amount of p-chloroaniline present (a substance that is produced when CHX is degraded).

Both formulations passed the stability test, and there was no significant difference in potency, pH, or purity. The potency of the gel formulation tended to decrease (although it remained within the acceptable range) probably because sufficient homogeneity was not achieved during laboratory testing without a proper homogenizer. In commercial production, this is unlikely to be an issue.

Based on these results on the stability of the product in this 6-month accelerated study, PATH estimates a 24-month shelf life at room temperature across all climatic zones listed above.

8. Cultivating Demand from Caregivers

Most of the recent work on CHX for umbilical cord care (Nepal, Pakistan, Bangladesh, Zambia, and Tanzania) has focused on community-level use of the product. In these contexts, some caregivers may have full medical training, but most are community health workers or TBAs. In each case, CHX for umbilical cord care has been well received when presented by program staff, with specific highlights in Table 11.

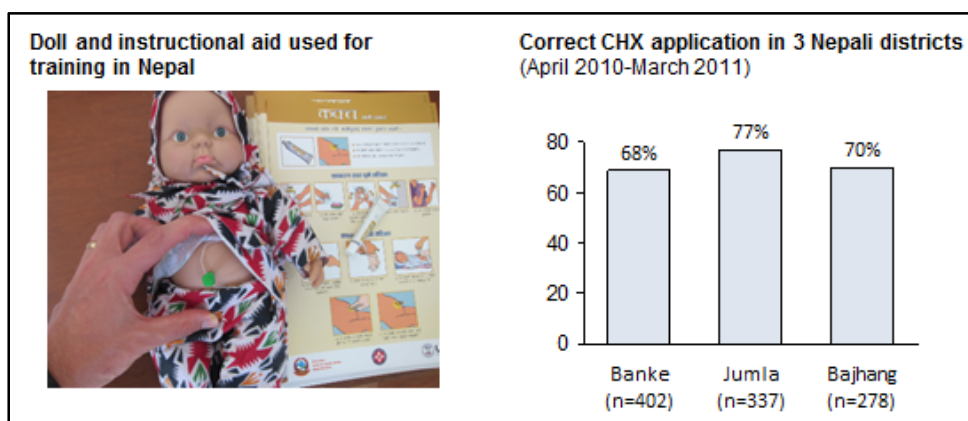
Table 11. Caregiver demand.

Location	Caregiver	Synthesis of comment or direct quotes
Pemba (Tanzania)	Unspecified	“We are willing to use it. Mothers can apply if they are trained.” “Most mothers will be willing to use this medicine. They pray for such thing to be introduced in the community as they are very useful.”
Bangladesh	TBA	TBAs were the single largest source of CHX, even when the product was both given away through government community outreach workers and sold in pharmacies. The TBAs appeared to appreciate the product as a special service they could offer (and potentially resell) to their clientele.
India	ASHA*	As part of government training, ASHAs are instructed to advocate for dry cord care in Uttar Pradesh. However, they are often frustrated by mothers who insist on dressing the cord in one way or another despite their advice. As dry cord care is unable to displace traditional practices, ASHAs are excited to recommend CHX as a way to finally have something to offer mothers in their communities.
Nepal	FCHV	FCHWs have enthusiastically embraced the product in the four districts where it is currently used today and have been able to ensure correct usage of CHX in close to 70% of all births in their catchment areas. Training is incorporated into existing FCHV training programs on other maternal and neonatal health topics.

*ASHA: Accredited Social Health Activist.

A critical component of cultivating caregiver demand has been training caregivers to understand the CHX product and administer it correctly. In Nepal, FCHVs were trained using dolls modified to have umbilical cords made from balloons as well as the instructional aide pictured below (Figure 4). In a follow-up study, FCHVs trained using these tools were able to ensure correct administration of CHX by household care-givers to roughly 70% of the newborns in their catchment areas.

Figure 4. Instructional aide and correct chlorhexidine application.



9. Cultivating Demand from Consumers

Discouraging mothers from putting anything on the cord has been a persistent challenge in communities around the world. Qualitative studies in India, Nepal, Uganda, Ghana, and Malawi show that mothers are often hesitant to leave the cord dry due to concerns that the cord might take longer to separate, cause the baby discomfort, or leave the baby vulnerable to various maladies. In fact, in Uttar Pradesh, India, despite government programs to promote dry cord care, 83% of mothers apply some substance to the cord.¹⁹ Formative work in Zambia and Pemba (Tanzania) also show that mothers have a strong desire to put something on the umbilical cord stump.

Specific motivations to dress the stump vary by region and by individual, but the most common reasons include a desire to make the cord stump separate faster and to prevent infection. The actual substances applied to the stump vary widely, sometimes even between individuals within the same community, but often fall into a few main categories:

- Edible oils and butters including ghee and shea butter, and mustard, palm, peanut, and coconut oils (India, Nepal, Bangladesh, Ethiopia, Mozambique, Tanzania, Nigeria, Zambia, and others areas).
- Medicinal products including powders, alcohols, iodine, and antibiotics (India, Ghana, Guinea Bissau, Malawi, Mozambique, Nigeria, Tanzania, Uganda, Zambia, and other areas).
- Waste products including animal feces, ash, dust, sand, dirt (India, Nepal, Nigeria, Tanzania, Zambia, Malawi, Uganda, and other areas).

Where studied, there appears to be a significant latent demand for purpose-built umbilical cord care products like CHX and often a willingness to displace existing practice with a product specifically packaged for this purpose. Mothers in many communities around the world are eager for a product to use in cord care and appear likely to adopt CHX once they are made aware of its existence.

10. Monitoring and Evaluation

There are several different ways to monitor and evaluate the transformation of CHX for umbilical cord care from being an overlooked commodity to status as a widely used intervention. A number of metrics (Table 12) may be useful in monitoring that progression and identifying where additional attention may be required.

¹⁹ Varma DS, Khan ME, Hazra A. Increasing postnatal care of mothers and newborns including follow-up cord care and thermal care in rural Uttar Pradesh. *Journal of Family Welfare*. 2010;56(special issue):31-41.

Table 12. Monitoring and evaluation metrics.

Supply Metrics	<ul style="list-style-type: none"> • Global monthly production volume of a 4% CHX product for neonatal use. • Geographic and demographic reach of manufacturers. • Quality of manufactured product.
Demand Metrics	<ul style="list-style-type: none"> • Number of countries recommending CHX for newborn care. • Volume of public tenders for CHX products. • % of public and private facilities with CHX in stock. • % of wholesale and retail pharmacies stocking CHX. • % of caregivers recommending the use of CHX. • % of consumers accepting CHX.
Correct-Use Metrics	<ul style="list-style-type: none"> • % of babies receiving CHX. • % of above within 2 hours of birth. • % of above where 3 g or more of product were used. • % of above where product was applied to the stump and surrounding areas. • % of mothers who report applying CHX and no other substance to the cord.
Impact Metrics	<ul style="list-style-type: none"> • Neonatal mortality rate. • Neonatal mortality from infection.

11. Recommendations

Several simple activities could increase the uptake and impact of chlorhexidine for umbilical cord care around the world:

- Add 4% chlorhexidine (7.1% chlorhexidine digluconate) for umbilical cord care to the WHO model list of essential medicines for children.
- Correct the common misconception that WHO advocates dry cord care only. The WHO umbilical cord care guidelines recommend that antimicrobials be used “...as a temporary measure, according to a local situation (e.g., in neonatal tetanus-endemic areas or to replace a harmful traditional substance).” These exceptions are rarely cited in discussions of WHO’s dry cord care recommendation but may apply to a more than half of all births around the world.
- Fast track registration of 4% chlorhexidine (7.1% chlorhexidine digluconate) for umbilical cord care with national regulatory authorities and encourage additional manufacturers to produce the drug with guaranteed minimum volumes.
- Train birth attendants to correctly apply chlorhexidine to the umbilical cord, as part of newborn care training programs.
- Allocate resources to integrate chlorhexidine for umbilical cord care into essential newborn care programs in order to generate sustainable demand and attractive manufacturing volumes for the product.

Through these actions, we are much more likely to see increased use of this overlooked intervention, thereby contributing to hundreds of thousands of newborn lives saved annually.

