

Frequently asked questions (FAQ) regarding use of 7.1% chlorhexidine digluconate for umbilical cord care

What is the evidence for using chlorhexidine for cord care?

Community-based randomized trials in rural areas in Bangladesh, Nepal, and Pakistan have shown that applying 7.1% chlorhexidine digluconate (delivering 4% chlorhexidine) to the umbilical cord stump prevents infection and saves newborn lives.^{1,2,3} These trials and concurrent research support chlorhexidine cord cleansing as an efficacious, acceptable, feasible, and cost-effective newborn care intervention.

Note that this intervention is sometimes confused with other chlorhexidine interventions around labor and delivery that have been investigated in recent years, notably vaginal cleansing of the mother and whole-body wiping of the newborn. These interventions have used a lower concentration and to date have not shown clear evidence of mortality reduction efficacy.

Is chlorhexidine safe to use on the umbilical cord?

Chlorhexidine is safe to use on the umbilical cord. There is a 40-year history of chlorhexidine application to the umbilical cord from developed countries, as well as widespread experience using chlorhexidine as a pre-surgical and an oral antiseptic. For umbilical cleansing, a concentration of 7.1% chlorhexidine digluconate was selected as sufficiently potent as an antiseptic, but at a low enough concentration not to represent a risk with regard to absorption into the bloodstream.⁴ As with many medicines intended for topical use, 7.1% chlorhexidine digluconate should not come into contact with eyes or ears.

How does chlorhexidine for cord care work?

Having tested chlorhexidine efficacy using a randomized controlled trial design—showing a similar mortality reduction effect across three trials—it is known that chlorhexidine for cord care works. This kind of epidemiologic study, however, does not give us a definitive explanation of *how* it works. Nevertheless, results to date certainly provide some insights. First, sepsis deaths arise without visible signs of infection at the cord stump, and such deaths are markedly reduced with use of chlorhexidine. Second, based on the disaggregated analysis of data from the Nepal trial, separating out those whose first chlorhexidine application was on the day of birth (among whom risk of death was 34% lower than controls) from those who started later (whose risk of death was no different than controls), it appears that it is the cord cleansing *on the day of birth* that is critical. This is confirmed by the results of the Bangladesh trial, which showed significant mortality reduction among those randomized to receive chlorhexidine application only on the day of birth.

These results suggest that chlorhexidine prevents sepsis deaths arising primarily through *direct bacterial seeding into the blood stream* through the freshly cut, still somewhat patent, cord vessels within the first

day or so after birth without ever showing any visible sign of cord infection. Although chlorhexidine application also has the effect of reducing frank infection to the cord stump and adjoining skin later in the first week and on into the second week of life, this appears to be a much less important mechanism for preventing infection deaths. It is also important to note that many of the children who die of infections that enter via the umbilicus never show signs of infection at the umbilicus.

What are the World Health Organization's guidelines on use of chlorhexidine for cord care?

In September 2012, the World Health Organization (WHO) held a consultation meeting with experts to review the evidence on use of chlorhexidine for cord care. The consultative meeting participants made the following recommendation to WHO:

Daily chlorhexidine 7.1% application to the umbilical cord stump over the first week of life is recommended for newborns who are born at home in settings with high neonatal mortality rate (NMR), greater than 30 deaths per 1000 live births.

For countries considering introduction of this intervention, the Chlorhexidine Working Group suggests countries and programs consider the following:

- The first day is the most important for application; additional use until the cord falls off has been shown to be beneficial.
- Data collected to date has been in home settings. Other programmatic considerations may also be important in developing a country strategy; for example, the typical hygiene conditions and amount of time a mother and child spend in a facility before discharge.
- This WHO guidance is based on data from settings with NMR >30. Countries may want to consider a regional approach to introduction depending on availability of data, or they may determine that the entire population could benefit from this life-saving intervention regardless of NMR.

Why should a program use chlorhexidine and not other antiseptics?

Chlorhexidine has a particularly favorable efficacy and safety profile compared to other antiseptics.⁴ Chlorhexidine was selected for the original mortality trial because of its broad-spectrum activity against gram-positive and gram-negative organisms, strong safety record with neonates of all gestational ages, strong binding to the skin for longer lasting antiseptic effect, and low cost. The formulation of chlorhexidine used in these trials is water-based whereas many antiseptics currently on the market are alcohol based. Iodine and alcohol are both contraindicated for premature babies. Gentian violet stains skin (hiding signs of infection) and is not active for gram-negative bacteria which can cause fatal infections. Although it is possible that other antiseptics could also work, we only have evidence for efficacy in reducing mortality risk for chlorhexidine.

What concentration of chlorhexidine should be used for cord care?

7.1% chlorhexidine digluconate (which delivers 4% chlorhexidine) is the recommended concentration for cord care. Chlorhexidine is available in different concentrations and may be more readily available in certain countries at 5% chlorhexidine digluconate (which delivers 2.1% chlorhexidine). The three

mortality trials conducted to date have all used 7.1% chlorhexidine digluconate, as are the two ongoing studies in Zambia and Tanzania. It is strongly recommended that chlorhexidine programs use a concentration of known efficacy (i.e., 7.1%), and this is what WHO is recommending.

What is the recommended regimen—single-day or multiple-day application?

The experts at WHO’s September 2012 consultation recommended multiple-day application.

However, some countries such as Nepal have selected to implement a single-day regimen. 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 multi-day application; that is what we have the most evidence for. However, in the original Nepal study a 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 controls. By contrast, those starting *on* the day of birth had one-third lower mortality. In the Bangladesh study, application only on day 1 was shown to reduce mortality risk; multi-day application had lower effectiveness—there wasn’t a statistically significant difference between multi-day and controls.

In the Pakistan study, the first application was done very early—by traditional birth attendants immediately after tying and cutting the cord. Subsequent applications were left to family members to attend to (i.e., fidelity was not assured to the same degree as for the first application). The mortality reduction effect size in the Pakistan study was higher than in the other two trials (38%). All three studies, in different ways, point to the importance of beginning applications as early as possible. While the day-of-birth applications are likely the most important, the trials have shown that multiple-day application provides additional benefit in preventing visible cord infection.

With evidence from the three trials, and considering messaging simplicity and cost, the Government of Nepal (which to date is the only country scaling up chlorhexidine use) has opted for single-day application. As other countries consider moving ahead with implementation, they will need to weigh the evidence, cost, and program considerations to decide how to proceed.

What is the expected impact in my country setting?

Expected impact will vary by setting depending on overall NMR and proportion of deaths actually due to bacterial infection. The effect size has varied across the three different settings where trials have been conducted to date (Bangladesh, Nepal, 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. In high-mortality settings (e.g., NMR >25/1000), bacterial infection is generally responsible for a large proportion of newborn deaths, and chlorhexidine could be expected to prevent many of them.

In countries with low neonatal mortality and where hygiene conditions around birth and the first days of life are reliably good, one would not expect a significant benefit.

Is chlorhexidine useful in countries where rates of cord infection and sepsis-related mortality are low?

The life-threatening cases of sepsis that appear to be prevented by chlorhexidine are generally not preceded by visible cord infection. Rates of cord infection are not necessarily a good indication of how effective chlorhexidine would be in reducing sepsis deaths.

Considering country-level, cause-specific mortality distribution estimates (for example, as made available in the Countdown coverage reports⁵ or Liu's recent paper⁶), sepsis may appear to account for around 15% of global newborn deaths. However, such analyses use algorithms that attribute sepsis deaths among premature newborns to prematurity rather than sepsis, which may underestimate the proportion preventable through use of an intervention like chlorhexidine. These analyses are indicative rather than precise estimates—they could be arguably lower or higher globally, nationally, and locally.

Is this intervention appropriate for deliveries in health facilities?

The experts at WHO's September 2012 consultation reviewed and made their recommendation based on data collected to date, which is from home settings. Absence of data for use in facility deliveries does not mean these settings should be excluded from use.

Chlorhexidine can be a critical prevention tool in maternity facilities where hygiene conditions and practices are questionable or where mothers and newborns are typically sent home within hours of delivery, increasing the chances that a newborn may be exposed to unhygienic conditions and practices during this critical early exposure window.

Have countries experienced challenges with the change in messaging from promotion of dry cord care to use of chlorhexidine?

No. Experience to date⁷ has been that in settings where other substances have traditionally been applied to the cord stump, messages recommending nothing be applied to the cord were widely ignored. When chlorhexidine has been made available in these same settings, its use largely displaced that of other substances and was an effective approach to discouraging application of other potentially harmful substances.

Where can I purchase chlorhexidine for my program?

There are two available sources for purchase of chlorhexidine at this time:

- Lomus Pharmaceuticals in Nepal (http://www.lomus.com.np/about_us.htm). They require a minimum lead time of 25 days.
- UNICEF Supply Division catalogue, product number S1531515 (<https://supply.unicef.org/>).

Local production of chlorhexidine is a worthwhile option in countries where there is a manufacturer already producing chlorhexidine products such as topical antiseptics. More information about local manufacturing of chlorhexidine for cord care is available on the chlorhexidine technical resource page: <http://www.healthynewbornnetwork.org/topic/chlorhexidine-umbilical-cord-care>.

How much does chlorhexidine cost?

The price of chlorhexidine for cord care will vary by country and manufacturer. For 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. Liquid 7.1% chlorhexidine digluconate is available from the UNICEF Supply Division catalogue for US\$0.36 for one 10-ml bottle.

Where can I learn more about chlorhexidine for umbilical cord care?

For more information about chlorhexidine for umbilical cord care, please visit the technical resource page: <http://www.healthynewbornnetwork.org/topic/chlorhexidine-umbilical-cord-care>.

Contact Information

For more information on introducing chlorhexidine in your country or for more information on this intervention, contact the **Chlorhexidine Working Group** at CHX@www.healthynewbornnetwork.org.

The Chlorhexidine Working Group is an international collaboration of organizations committed to advancing the use of 7.1% chlorhexidine digluconate (delivering 4% chlorhexidine) for umbilical cord care through advocacy and technical assistance. PATH is the Secretariat of the CWG, and members include individuals representing (alphabetically): Bill & Melinda Gates Foundation; Boston University; Jhpiego; Johns Hopkins Bloomberg School of Public Health; John Snow, Inc.; the Maternal and Child Health Integrated Program; Promoting the Quality of Medicines in Developing Countries project/United States Pharmacopeia; PSI; Save the Children/Saving Newborn Lives program; Systems for Improved Access to Pharmaceuticals and Services Program/ Management Sciences for Health; the United States Agency for International Development; United Nations Children’s Fund; and Venture Strategies Innovations.

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