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Safety and Impact of Chlorhexidine Antisepsis Interventions for Improving Neonatal Health in Developing Countries

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Abstract

Affordable, efficacious, and safe interventions to prevent infections and improve neonatal survival in low-resource settings are needed. Chlorhexidine is a broad-spectrum antiseptic that has been used extensively for many decades in hospital and other clinical settings. It has also been given as maternal vaginal lavage, full-body newborn skin cleansing, and/or umbilical cord cleansing to prevent infection in neonates. Recent evidence suggests that these chlorhexidine interventions may have significant public health impact on the burden of neonatal infection and mortality in developing countries. This review examines the available data from randomized and nonrandomized studies of chlorhexidine cleansing, with a primary focus on potential uses in low-resource settings. Safety issues related to chlorhexidine use in newborns are reviewed, and future research priorities for chlorhexidine interventions for neonatal health in developing countries are discussed.

We conclude that maternal vaginal cleansing combined with newborn skin cleansing could reduce neonatal infections and mortality in hospitals of sub-Saharan Africa, but the individual impact of these interventions must be determined, particularly in community settings. There is evidence for a protective benefit of newborn skin and umbilical cord cleansing with chlorhexidine in the community in south Asia. Effectiveness trials in that region are required to address the feasibility of community-based delivery methods such as incorporating these interventions into clean birth kits or training programs for minimally skilled delivery assistants or family members. Efficacy trials for all chlorhexidine interventions are needed in low-resource settings in Africa, and the benefit of maternal vaginal cleansing beyond that provided by newborn skin cleansing needs to be determined.

Keywords

chlorhexidine; cleansing; infection; neonatal; mortality; omphalitis; skin infection; superficial infection; umbilical cord

Of the 4 million annual neonatal deaths that occur globally, more than 99% occur in developing countries and approximately 36% are attributed to infections.[1] In communities with high neonatal mortality rates, infections account for approximately half of all newborn deaths.[1,2] Infection risk is high because many infants are born at home, where deliveries are often conducted by unskilled birth attendants; care provided during labor, delivery, and the immediate postnatal period is often unhygienic or includes harmful practices; rates of low-birth-weight and preterm birth are high; and access to functioning health systems that can effectively recognize and manage infection is limited in many communities. Continued efforts are required to describe optimal community-based delivery of proven interventions[3] and to

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identify new, affordable, efficacious, and safe interventions to prevent infections in low-resource settings.

There is evidence that delivery of chlorhexidine solutions by vaginal lavage during labor and delivery, full-body newborn skin cleansing, and/or umbilical cord cleansing reduces neonatal bacterial colonization, infection and mortality.[4–7] Research on chlorhexidine use in newborns in developed countries has focused mainly on antisepsis of central venous catheters,[8–10] as well as prevention of vertical transfer of microorganisms, especially group B streptococcus (GBS), from mother to newborn at the time of delivery.[11,12] In developing countries, investigators have examined the potential of chlorhexidine vaginal cleansing to reduce vertical transmission of HIV and prevent neonatal morbidity and mortality.[4,5] The evidence for impact of intrapartum vaginal cleansing with chlorhexidine on vertical transmission of HIV,[13] neonatal colonization and infection with GBS,[14] and on other infections[15] has been reviewed by Cochrane meta-analyses. The strict inclusion criteria for those reviews, however, limited consideration to a small number of studies, and the focus on vaginal cleansing has failed to address the potential impact of nonvaginal chlorhexidine-based interventions such as newborn skin and umbilical cord cleansing.

This paper reviews the literature on chlorhexidine interventions (vaginal, newborn skin and umbilical cord cleansing) with a focus on neonatal outcomes. We review safety issues pertaining to the use of chlorhexidine in newborns and describe the use of chlorhexidine in low-resource settings, including studies from developing countries of varied design. Lessons learned from studies in developed countries are included to inform the design, delivery, and potential impact of chlorhexidine interventions in low-resource environments. Gaps in research are described and an outline for future research priorities for chlorhexidine interventions for neonatal health is presented.

SAFETY OF CHLORHEXIDINE

Chlorhexidine, a broad-spectrum antiseptic, is effective against a wide range of both Gram-positive and Gram-negative bacteria, including major agents of neonatal sepsis, as well as some viruses, including HIV.[16] Since its synthesis in 1950, chlorhexidine has been used for many years in hospital and other clinical settings for hand and wound cleansing and skin and mucosal antisepsis before surgery or other procedures that penetrate these barriers. Common formulations of chlorhexidine include aqueous and alcohol-based solutions, gels, and powders; all have been used topically on adult, infant and neonatal skin.

Compared with the widespread use of chlorhexidine, reported side effects have been few and have included delayed reactions such as contact dermatitis and photosensitivity, toxicity as a result of inadvertent application to the ear with access to the inner ear through a perforated tympanic membrane, and, in very rare cases, hypersensitivity reactions such as anaphylactic shock.[17] The record of use and safety in the general population has been reported previously.[16,18]

Contact dermatitis was reported in 5% of preterm (< 28 weeks' gestation) extremely low-birth-weight (< 1000 g) infants after long-term (> 7 days) placement of chlorhexidine-impregnated dressings for central venous catheters.[9] The effect may have been caused by the occlusive placement of the dressing rather than the chlorhexidine itself; in the same study, no infants receiving a preplacement scrub with 0.5% chlorhexidine developed dermatitis. Contact dermatitis has not been reported in infants receiving full-body wiping, bathing, or umbilical cord cleansing with chlorhexidine. Transient bradycardia was reported in a breast-fed infant whose mother's breast was sprayed with chlorhexidine.[19]

After the discontinuation of hexaclorophane use in the early 1970s,[20] bathing of newborns in chlorhexidine-based solutions quickly became routine practice in many clinical settings to reduce the occurrence of staphylococcal outbreaks in nurseries.[18,21,22] Studies were undertaken in the 1970s and 1980s to investigate the potential for percutaneous absorption or adverse events after neonatal skin or umbilical cleansing with chlorhexidine (Table 1).

ABSORPTION OF CHLORHEXIDINE

Newborn Skin Cleansing

After daily bathing of newborns (n = 34; 29 preterm) for up to 32 consecutive days, while hospitalized, with 4.0% chlorhexidine (Hibiscrub),[23] heel prick samples taken from the first 10 infants were positive for chlorhexidine (Table 1). Investigators suggested that the samples were contaminated from residual chlorhexidine on the skin and collected venous blood samples from the remaining 24 infants. Among these, 5 had detectable chlorhexidine, and all were less than 36 weeks' gestational age at the time of cleansing and were likely to have increased epidermal permeability because of immature skin development.[24] There was no indication that the low levels of chlorhexidine detected in the blood samples resulted in any harmful effects.

No chlorhexidine was detected in blood samples collected after full-body bathing of 41 full-term infants 1−3 times with a 0.4% chlorhexidine solution.[25] Fifty full-term infants were bathed daily for 3 days with 4% chlorhexidine, and heel prick samples taken on each day 1 hour after bathing were negative[26]; infants were followed up after 1 year, and no long-term adverse effects of the bathing were recorded. In a recent hospital-based study in South Africa, chlorhexidine was detected in sera of 30% (3/10) and 10% (1/10) of infants receiving a single bath with 1% or 2% chlorhexidine, respectively.[27]

Umbilical Cord Cleansing

Among 44 infants (23 vaginal, 21 cesarean delivery) who received 9 consecutive days of cord cleansing with 4.0% chlorhexidine, day 5 serum samples from all but 1 infant were negative[28] (Table 1). Contamination from the skin surface could not be ruled out because this infant was vaginally delivered and mothers underwent chlorhexidine cleansing of the perineum and vulva before delivery. In an earlier study, full-term and preterm infants received daily umbilical cord cleansing with 1.0% chlorhexidine in ethanol.[29] After 9 days, median levels of detectable chlorhexidine in blood were higher among preterm (n = 23; 32 ng/mL) than full-term infants (n = 25; 0 ng/mL); however, the proportion of infants with detectable chlorhexidine was not reported. A subsequent group of 29 infants was given 1.0% chlorhexidine in a nonethanol formulation; of these, 4 (14%) had detectable chlorhexidine, and 3 of these had had umbilical cord catheters treated with the ethanolf-based formulation.

Clinical Evidence of Adverse Effects in Neonates

Larger studies of the impact of chlorhexidine interventions on neonatal outcomes have not measured absorption in newborns but provide for further review of its safety record. Repeated vaginal flushings with 0.2% chlorhexidine during delivery were given to 2283 women to assess the effect of vaginal disinfection with chlorhexidine on neonatal morbidity. No adverse events were reported in babies born to mothers in the intervention group.[11] Vaginal cleansing with chlorhexidine during labor has been well tolerated by newborn infants in numerous other studies with hundreds of mother-baby pairs.[12,30–36]

Investigators from Malawi[4] and Egypt[5] have implemented intrapartum vaginal lavage and full-body newborn skin cleansing with 0.25% chlorhexidine. In those studies combined, more than 6000 infants received the intervention without any reported adverse events. We recently

examined newborn skin cleansing alone in a community-based study in rural Nepal.[6] More than 8500 newborns were cleansed soon after birth (median time 5.8 hours) with a baby wipe that released 0.25% chlorhexidine (0.44% chlorhexidine digluconate) to the skin without any reported adverse events. Topical applications of 4.0% chlorhexidine (7.1% chlorhexidine digluconate) to the umbilical cord during the first 10 days of life were well tolerated by approximately 5000 infants in Nepal.[7] Cleansing of the cord with 4.0% chlorhexidine has been implemented routinely in many clinical settings throughout the world for the past 4 decades and is considered safe.[37]

Summary of Chlorhexidine Safety

In summary, after topical applications of chlorhexidine, some percutaneous absorption occurs, particularly in preterm newborns, but only at trace levels. The data on safety, however, are incomplete. For example, the concentration of chlorhexidine used for multiple different interventions spans a wide range. Although the concentrations reported thus far appear to be safe, the upper level of chlorhexidine that can be considered safe is not known; Wilson and colleagues[27] have suggested that 1% is the highest tolerable concentration for vaginal and newborn skin cleansing. Some areas of the body have higher vascularity (such as the face and scalp), and when included in skin cleansing regimens, these sites may have higher absorption; no site-specific safety data, however, exist. In general, the potential for absorption appears to be reduced when chlorhexidine is applied in aqueous or other nonethanol-based formulations. There are no reports of adverse health consequences as a result of absorption of chlorhexidine in neonates, and there is no reason to suspect 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 thus use of chlorhexidine-based interventions in these infants should be monitored carefully. Tens of thousands of neonates have received a range of chlorhexidine-based cleansing interventions including vaginal lavage, full-body cleansing, and umbilical cord cleansing, without reported adverse effects.

IMPACT OF CHLORHEXIDINE INTERVENTIONS

Many studies have examined the impact of chlorhexidine interventions on neonatal health. The results and conclusions of these investigations of vaginal, skin, and umbilical cord cleansing are discussed separately below.

Vaginal Cleansing

GBS Colonization and Infection—GBS is the major cause of early- and late-onset neonatal sepsis in full-term infants in developed countries. Intrapartum chemoprophylaxis and multivalent conjugate vaccines reduce neonatal colonization and the risk of early-onset sepsis.[38] Costs, shifting serotypes, and lack of skilled personnel, however, have impeded widespread implementation of these strategies, particularly in low-resource settings.

Vaginal cleansing with chlorhexidine before or during delivery prevents vertical transfer of GBS to the neonate. The Swedish Chlorhexidine Study Group explored the minimum inhibitory and bactericidal concentrations of chlorhexidine,[39] described postcleansing vaginal concentrations of chlorhexidine and its residual effect on GBS carriage,[40,41] and demonstrated that trace levels of chlorhexidine could be absorbed through the vaginal mucosa.[42] Pilot studies showed that vaginal washing with chlorhexidine reduced newborn colonization with GBS compared with those born to nonwashed controls.[43,44] These studies prompted a series of large randomized controlled trials with varying vaginal cleansing protocols for further exploration of the potential of this intervention to reduce GBS-related neonatal morbidity (Table 2).

Two trials[11,34] demonstrated reductions in vertical transfer of GBS, admissions to the neonatal intensive care unit, and neonatal infections. A third study confirmed that vaginal disinfection reduced GBS colonization of the newborn, but hospital admissions, cases of probable infection, and mortality were equal between the groups.[12] Conducting vaginal examinations during labor using surgical gloves lubricated with 1.0% chlorhexidine digluconate cream did not provide protection against vertical transfer of GBS compared with the use of nonlubricated gloves.[45]

Although these data indicate that vaginal disinfection may reduce neonatal colonization with GBS, the low overall rates of early-onset GBS sepsis has precluded estimation of the impact on newborn infection. None of these studies was conducted in developing countries, and the validity of extrapolating the potential benefit to such settings is problematic. GBS generally has not been identified as a major neonatal pathogen in developing countries, especially in South Asia. In some settings, however, vaginal colonization rates among women are similar to those in industrialized countries.[46] Because the majority of births occur outside of health facilities, the impact of maternal GBS colonization and vertical transfer may be underappreciated, yet further research is required.

Vaginal cleansing with chlorhexidine reduces vertical transmission of GBS to the same degree as intrapartum antibiotics[47] and may be significantly cheaper and easier to implement in settings where skilled providers are lacking. Additionally, the antibacterial action of chlorhexidine extends beyond GBS to a broad spectrum of potentially invasive pathogens. In developing countries where sepsis rates in general are significantly higher, vaginal cleansing interventions have the potential to affect a wider range of neonatal infections.

All-Cause Neonatal Infection—The impact of chlorhexidine-based vaginal cleansing interventions on other neonatal outcomes, including vertical transfer of HIV, newborn bacterial colonization, morbidity, and mortality due to non-GBS pathogens has been studied in both developed and developing countries (Table 3). Five of the studies in Table 3 were conducted in developed countries (United Kingdom, Norway, United States). Stray-Pederson et al[34] found a significant reduction in infectious morbidity (4.9% versus 7.9%, $P < 0.05$), whereas Calkin[31] found no differences in the rate of admissions to the special-care baby unit among newborns born to chlorhexidine-treated women.

Three other studies from developed countries[32,33,35] focused primarily on maternal outcomes but also reported secondary neonatal outcomes. Details of these studies are found in a Cochrane review[15] on the impact of vaginal cleansing with chlorhexidine on neonatal infection. The low incidence of any type of neonatal infection precluded an accurate estimate of the impact of this intervention, either within studies or when combined in the Cochrane review.[15] In the combined analysis for neonatal sepsis, the relative risk (RR) of infection among the chlorhexidine group was 0.75 (0.17−3.35).[15] Slightly more evidence exists if pneumonia, sepsis, and meningitis infections are combined (RR = 0.54 [0.15−1.97]). Thus, although incidence was low, there was a nonsignificant trend toward more infections in the control groups of these studies (Table 3), suggesting that the utility of this intervention might be examined in low-resource settings where neonates have higher risk of infection and mortality.

Three large studies of vaginal cleansing with chlorhexidine during labor have been undertaken in hospitals in developing countries (Table 3). The original motivation for examining this intervention in sub-Saharan Africa was to prevent mother-to-child transmission of HIV. In a Kenyan hospital, when mothers received vaginal lavage with 0.2% chlorhexidine (later increased to 0.4%), the overall rate of vertical HIV transmission was similar in the intervention and nonintervention periods.[36] These findings were largely consistent with a prior hospital-based study in Malawi.[48] An important difference between the studies was that newborn infants in the intervention arm of the Malawi trial were also given full-body cleansing with

0.25% chlorhexidine. This design, combining both vaginal disinfection and newborn skin cleansing with chlorhexidine and comparing with no intervention, was recently replicated in a hospital in Egypt.[5] These studies and the impact of this dual intervention on neonatal infection and mortality are discussed in more detail in the following section.

FULL-BODY NEONATAL SKIN CLEANSING

In the past, full-body cleansing of newborn infants with antiseptic agents was commonplace, although the practice has diminished in recent decades because of the promotion of dry skin care.[49] Despite the widespread use of antiseptic bathing or washing, there have been few reports of the impact of chlorhexidine skin cleansing on neonatal infections (Table 4).

Developed-Country Studies

In a comparative audit of periods in a hospital before and after implementing full-body washing with 0.4% chlorhexidine, there were fewer superficial infections (eye, skin, umbilical) among ~6000 infants receiving a chlorhexidine bath[21] (Table 4). A small randomized trial conducted in 2 hospitals in Sweden similarly reported that daily full-body cleansing of newborns with 4.0% chlorhexidine until discharge reduced superficial infections during the first 6 weeks of life.[50] Infants in that study, however, also received daily applications of 4.0% chlorhexidine to the umbilical cord.

Developing-Country Studies

Two hospital-based studies conducted in developing countries[4,5] combined vaginal and neonatal skin cleansing with chlorhexidine (Table 4). In both studies, attendants wiped the birth canal and external genitalia using chlorhexidine-soaked cotton swabs wrapped around the examining fingers, and infants were wiped all over the body using cotton pads soaked in 0.25% chlorhexidine. Outcomes during 1 or more periods of intervention were compared with those during nonintervention periods. In the Malawi study, overall admissions (19.3% to 16.9%, $P < 0.01$) and admissions for neonatal sepsis (7.8 versus 17.9 per 1000, $P < 0.001$) were reduced in the intervention period. Furthermore, there were reductions in all-cause (22% reduction; 28.6 versus 36 per 1000, $P = 0.06$) and infection-specific neonatal mortality (68% reduction; 2.4 versus 7.3 per 1000, $P < 0.01$). In the Egypt study, while the overall rate of admissions to the NICU were similar in both groups, admissions due to infection, all-cause mortality, and infectious mortality were significantly reduced among infants in the intervention arm.[5]

In neither of these trials was it possible to determine the independent effects of vaginal and neonatal skin cleansing on infection and mortality. The only large-scale trial to examine this intervention in the absence of vaginal cleansing was conducted in a community in southern Nepal[6] (Table 4). At this site, where 95% of infants are born at home, local female project workers were trained to wipe infants (entire body, excluding eyes/ears) in the home soon after birth using prepackaged 0.25% chlorhexidine or placebo baby wipes. Among infants of low birth weight, neonatal mortality was reduced by 28% (RR = 0.72 [0.55−0.95]), whereas there was little evidence of any difference in mortality risk among normal-weight (≥2500 g) infants (RR = 1.20 [0.80−1.81]). Given that this is the only large-scale trial of community-based newborn skin cleansing, further research is needed before promoting broad implementation of the intervention. The results from the Nepal trial, however, do suggest that full-body cleansing with chlorhexidine at birth may offer an important protective benefit, especially for low-birth-weight or preterm infants with compromised skin barrier function who may be at high risk for acquisition of infection via percutaneous invasion.[51–54]

UMBILICAL CORD CLEANSING

Topical applications of chlorhexidine to the umbilical cord stump might also improve neonatal health outcomes in developing countries. The current WHO recommendation for dry cord care[55] is based largely on a Cochrane review that concluded there was insufficient evidence to recommend topical antiseptics for prevention of umbilical cord infection (RR = 0.53 [0.25 −1.13]).[56] Of 21 studies included in the most recent version of the review, only 7 reported cord infection, and the overall rate of infection was low. One study included chlorhexidine as one of the treatment groups,[50] and no deaths were reported in any of the studies, limiting the extent to which the systematic review can inform decision-making about optimal cord care practices.

Developed-Country Studies

There are many published reports of the use of chlorhexidine at various concentrations for umbilical cord cleansing, but most do not include infections[56–60] and are not included in this review. Studies comparing the impact of chlorhexidine cord care regimens on infection (eye, skin, umbilical) and/or mortality are included in Table 5. Four of the studies are from developed countries (Norway, Sweden, New Zealand), and only 1[50] met the criteria for inclusion in the Cochrane review. These studies as a group, however, suggest that 4.0% chlorhexidine can reduce the risk of omphalitis and other superficial infections of the eye and skin. In a comparison with 580 retrospective controls receiving dry cord care, the proportion of infants in a Swedish nursery with *S. aureus* infections was reduced from 16.2% to 2.9% after 4.0% chlorhexidine cleansing of the cord.[61] In a second site, the incidence of omphalitis was significantly reduced among those treated with 4.0% chlorhexidine compared with 70% ethanol. Similar decreases in superficial infections associated with the use of 4.0% chlorhexidine have been reported.[50,62,63] A review of topical applications of antiseptics to the umbilical cord noted the strong evidence for reductions in bacterial colonization after chlorhexidine treatment of the cord and highlighted the need for further investigations with 4.0% chlorhexidine in developing-country settings.[37]

Developing-Country Studies

We recently reported on the first community-based randomized trial of the impact of chlorhexidine cleansing on umbilical cord infection.[7] In southern Nepal, more than 15,000 infants were randomized to receive umbilical cord cleansing during the first 10 days of life with (1) 4.0% chlorhexidine, (2) soap-and-water solution or (3) dry cord care. A number of sign-based algorithms[64] for defining omphalitis were used to examine the impact of chlorhexidine on cord infections. In the chlorhexidine group, incidence of mild and severe omphalitis was reduced significantly by 32% (RR = 0.68 [0.58, 0.80]) and 75% (RR = 0.25 [0.12, 0.53]), respectively. Soap-and-water cleansing had no protective benefit. Overall neonatal mortality was reduced by 24% among the group receiving chlorhexidine. The impact on mortality was stronger among infants who received cleansing within 24 hours of birth (RR = 0.66 [0.46, 0.95]).

FUTURE RESEARCH

Although the potential impact of chlorhexidine-based interventions has been demonstrated in a number of studies discussed above, there have been few well-designed studies in low-resource settings. Given the burden of neonatal mortality in communities of developing countries, there is a need for simple interventions to reduce this burden.[3] A single wipe of the newborn after birth can be conducted safely in the community,[65] and the potential for considerable impact of chlorhexidine cleansing of the umbilical cord and skin of newborns in the community[6,7] represents an important public health opportunity. Community-based studies, however, are the

exception, and before policy changes are recommended, further work is required. Apart from the Nepal studies, no other community-based studies of the impact of any chlorhexidine cleansing intervention have been conducted in regions where neonatal mortality risk remains high, such as Africa or Latin America, or elsewhere in Asia. Proposed efficacy, effectiveness, and operational research priorities for the 3 types of chlorhexidine interventions are discussed below.

Vaginal Cleansing

The 2 large facility-based studies from Africa[4,5] indicate that vaginal cleansing may improve neonatal outcomes, but neither study used a randomized design and as such have not been widely accepted. To overcome this weakness, randomized studies in South Africa, Pakistan, and Zimbabwe have been designed and are in implementation; these may provide additional information on the effectiveness of this intervention in facilities. Both of the prior studies and these ongoing trials, however, use the combined vaginal and newborn skin cleansing intervention in a single arm. These studies do not allow estimation of the relative contribution of each of the components of the dual intervention.

Within facilities, separating these individual effects is of less importance because the vaginal and newborn skin cleansing can be easily delivered together. In the community, however, given the potential barriers to implementing vaginal cleansing at the household level and the large proportion of births that occur in the home, there is a need to determine the additional benefit of maternal vaginal cleansing over and above that provided by newborn skin cleansing. The impact of vaginal cleansing might be modified by setting; for example, where ascending infections play a more prominent role in early neonatal sepsis, the combined intervention make take on increased importance.

The design of large community-based trials of vaginal cleansing in developing countries would benefit from further comparative studies of alternative cleansing methods such as vaginal lavage, wiping the birth canal with chlorhexidine-soaked cotton gauze, gel applications, or others. Henrichsen et al[30] found no differences in the rates of probable neonatal sepsis comparing vaginal disinfection with gel or aqueous formulations of chlorhexidine. Others, however, have suggested that gel-based chlorhexidine methods might have increased residual effect or be more resistant to inactivation by amniotic fluid or blood.[12] Issues regarding acceptability, ease of use, level of skill required for implementation, and the feasibility of delivering the intervention in the home need to be explored.

Newborn Skin Cleansing

Although newborn skin cleansing with chlorhexidine demonstrated significantly reduced mortality among low-birth-weight infants,[6] considerable work is required to understand the mechanism(s) through which this intervention acts on infection and mortality. For example, what is the relative importance of reducing bacterial colonization, altering the local microbial balance and/or improvements in skin barrier function? These and other questions could be investigated concurrently within an efficacy trial to replicate these results in another south Asian setting. If replicate studies show similar results, community-based effectiveness studies might examine the delivery of the simple cleansing intervention by minimally trained community-health workers, traditional birth attendants and/or caretakers in the home. Concurrent trials in more controlled, laboratory, and/or hospital-based settings might also provide insight into potential mechanisms for effect of skin cleansing on neonatal mortality.

In non-South Asian settings, newborn skin cleansing should be examined in the community, comparing chlorhexidine cleansing with water-based placebo or no cleansing. We would

advocate that such a study also include a third group allocated to both maternal vaginal cleansing and newborn cleansing to determine the additional benefit of vaginal cleansing.

For future trials of efficacy and effectiveness in community settings, a number of technical questions should be answered regarding optimal delivery methods for chlorhexidine. Soft wipes impregnated with chlorhexidine could be prepackaged and delivered as part of an enhanced clean birth kit. Can quality control of locally made products ensure their safety and efficacy (ie, will these wipes reliably and reproducibly release the proper concentration of active ingredient onto the skin)? Can chlorhexidine be formulated as a lotion and applied manually rather than via an impregnated cloth, with retention of efficacy? What is the feasibility of including the product in a clean delivery kit, and will this have additional benefits by increasing demand for kit use and thus, coverage of other effective interventions such as use of a clean blade? What is the optimal concentration of chlorhexidine for newborn skin cleansing?

Umbilical Cord Cleansing

Among the 3 interventions, umbilical cord cleansing with 4.0% chlorhexidine, overall, appears to be the most simple and affordable and closest to being ready for routine programmatic use. The high concentration is safe and is highly bactericidal, thus minimizing the risk of contamination of the product. Further research is needed to determine the number of applications to the cord required to achieve mortality reductions, and operational research is necessary to identify the requisite skills to effectively apply the intervention. For example, could a small vial of 4% chlorhexidine in a clean delivery kit be effectively applied using a sterile, low-cost applicator (eg, cotton ball) by unskilled birth attendants or mothers? An effectiveness study for the community setting would be appropriate for answering these questions. Cord cleansing solutions could be offered as part of an enhanced clean delivery kit, distributed to mothers and/or other caretakers during antenatal visits, or included in community-health worker or traditional birth attendant training programs.

There are no data available on cord cleansing from facilities or communities in Africa or Latin America, or from health facilities in Asia, and efficacy trials in these contexts are needed. Although neonatal mortality should be a primary outcome, the impact on umbilical cord infection should also be measured using sign-based definitions for omphalitis that can be reliably and consistently applied by minimally skilled health workers.[64] Further research is needed, however, to validate the use of clinical algorithms for identifying cord infections in African populations.

For vaginal, full-body skin cleansing, and cord cleansing, more information is needed on the cost of delivering the chlorhexidine-based interventions under a variety of conditions. The cost of the chlorhexidine itself is relatively low. For example, in our recent study in Nepal, the chlorhexidine cost to provide cord or full-body cleansing to a single infant was approximately $0.07 and $0.04, respectively. The substrate for wipe cloths, manufacturing, packaging, and shipping can all add significantly to the cost, although these may be minimized by using local materials and processing. Future facility- or community-based effectiveness studies of vaginal, skin, and umbilical cord cleansing should include detailed cost-effectiveness analyses to assist in policy decisions regarding the feasibility of chlorhexidine-based interventions.

CONCLUSIONS

Chlorhexidine-based antisepsis interventions have the potential for significant reduction of the burden of neonatal morbidity and mortality in developing countries, yet further information is needed before policy recommendations can be made. Effectiveness studies and subsequent scaling up of these interventions and incorporation into maternal and neonatal health programs

require a shift in our perspective on newborn washing and optimal care practices. For example, the WHO currently recommends no bathing/washing of infants within the first 6 hours after birth and dry cord care for the umbilical cord stump. In the absence of sufficient documented evidence from developing countries, policymakers have been forced to shape recommendations based on often limited information from developed countries. As continued research into chlorhexidine cleansing interventions provides information on the impact in facilities and communities of developing countries, researchers, program managers, and policymakers should work together to revisit these recommendations, using the full range of available evidence to shape informed policies that maximize the potential of these interventions.

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TABLE 1

Studies of Absorption of Chlorhexidine After Skin or Umbilical Cord Cleansing of Neonates

Study	Chlorhexidine Delivery Method	Concentration and Application	Sample Size*	Sample Collection Method	# Measured	# (%) With Detectable Chlorhexidine	Range (ng/mL)
Newborn skin cleansing							
Cowen[23] (UK, 1977)	Skin cleansing; nurses applied cleanser with hand daily	4.0% ChxD	10 Preterm	Heel Prick	10	10 (100)	53–1021
			21 Preterm	Venous	21	5 (25)	91–460
			3 Term	Venous	3	0 (0)	—
O'Neill[25] (USA, 1982)	Skin cleansing; applied (30 mL) with sterile washcloth	0.4% ChxD	41	Venous	41	0 (0)	—
O'Brien[26] (USA, 1984)	Full-body bathing for 3 d	4.0% ChxD	50 Full-term	Heel Prick	50	0 (0)	—
Wilson[27] (South Africa, 2004)	Skin cleansing; aqueous solution applied with soaked cotton balls	0.25% ChxD	27	Venous	0	—	—
		1.0% ChxD	82		10	3 (30)	13–26
		2.0% ChxD	88		10	1 (10)	27
Umbilical cord cleansing							
Aggett[29] (UK 1981)	Umbilical cord cleansing; 3 times daily for 9 d	1.0% ChxE + 1.0% ChxZO	25 Term	Venous	25	—	0†
		1.0% ChxE + 1.0% ChxZO	23 Preterm		23	—	32†
		1.0% ChxZO	29 Preterm		29	4 (14)	16–92
Johnsson[28] (Sweden, 1987)	Umbilical cord cleansing; applied daily to cord stump and periumbilical area	4.0% ChxD	32 Vaginal	Venous	23	1 (4)	496
			36 C-section		21	0 (0)	—

ChxD, chlorhexidine digluconate; ChxE, chlorhexidine in ethanol; ChxZO, dusting powder containing chlorhexidine in zinc oxide (3%).

*Sample size indicates number of infants receiving treatment with chlorhexidine, not sample size for the entire study.

†Median level.

TABLE 2

Studies of the Impact of Vaginal Cleansing With Chlorhexidine (chx) on Group B *Streptococcus* Colonization and Infection in Neonates

Study	Design	Objective/Outcome(S)	Chlorhexidine Dose and Delivery Method	Sample Size	Results
Christensen[23] (Sweden, 1985)	Nonrandomized trial	Impact of vaginal washing with chx on vertical transmission of GBS	Single vaginal wipe with 0.2% chlorhexidine	19 chx 41 Controls	Reduced GBS colonization of infants from 39% (16/41) to 11% (2/19) OR = 0.18 (0.02−0.97)
Kollee[44] (Netherlands, 1989)	Nonrandomized trial	Impact of vaginal chx disinfection on vertical transmission of GBS	0.3% chx gel every 10 h (no-treatment control)	(73 GBS carriers) 17 chx gel 56 No treatment	Vertical transmission of GBS was 50% in those not receiving treatment (27/56), whereas 0% of infants born to women receiving treatment were colonized (0/17) ($P < 0.001$)
Burman[11] (Sweden, 1992)	Multihospital randomized controlled trial	Impact of vaginal chx disinfection on vertical transmission of GBS, rate of admissions to the NICU, and neonatal infections	60 mL 0.2% chx Diacetate flushing every 6 h (saline placebo control)	2238 Intervention 2245 Control	Among infants born to colonized women, chx flushing reduced admission to the NICU (RR = 1.95 [0.94−4.03]); infectious morbidity (respiratory disorders, probable or diagnosed infection) was reduced in the chx group (RR = 3.15 [1.08 −9.22])
Adriaanse[12] (Netherlands, 1995)	Randomized controlled trial	Impact of vaginal chx disinfection on vertical GBS transmission and GBS disease	0.3% chx gel every 10 h (placebo gel control, no treatment control)	327 chx 328 Placebo 326 No treatment	Among infants born to GBS carriers, chx gel reduced vertical transmission of GBS ($P = 0.026$); no difference in infectious morbidity was found between groups
Hennequin[45] (Belgium, 1995)	Randomized controlled trial	Impact of vaginal chx disinfection on vertical transmission of GBS	Vaginal examinations conducted with surgical gloves lubricated with 5 mL of 1% chx cream (nonlubricated gloves in control group)	(59 GBS carriers) 28 chx 31 Control	Vertical transmission of GBS was the same in both groups (39% vs. 42%) ($P = 0.836$)
Stray-Pederson[34] (Norway, 1999)	Randomized controlled trial, plus reference comparison period	Impact of vaginal cleansing with chx on vertical transmission of GBS and subsequent neonatal infectious morbidity	120 mL of aqueous 0.2% chx flushing every 6 h (saline placebo control)	550 chx 586 Saline 867 Reference	Among infants born to GBS carrier women, chx flushing reduced GBS vertical transmission compared to saline and retrospective controls ($P = 0.02$). Reduction in overall infectious morbidity, including GBS was found (4.9% vs. 7.9%, $P < 0.05$)

TABLE 3

Studies of the Impact of Vaginal Cleansing With Chlorhexidine (chx) on Morbidity and Mortality in Neonates

Study	Design	Objective/Outcome(S)	Chlorhexidine Dose and Delivery Method	Sample Size	Results
Developed countries (all hospital based)					
Rouse[33] (USA, 1997)	Randomized controlled trial	Impact of chx flusing on: Maternal peripartum infection; neonatal infections (sepsis, mortality)	Single vaginal flushing with 200 mL of 0.2% chx (200 mL sterile water control)	512 chx 518 Control	No difference in sepsis rates between the 2 groups (total of 2 cases [0.4%] in each group, RR = 1.01 [0.14−7.15]). No impact on mortality (1 death in control group, not related to intervention)
Rouse[35] (USA, 2003)	Randomized controlled trial	Impact of chx flushing on: Maternal peripartum infection; neonatal infections (sepsis, antibiotics, NICU admissions, mortality)	Vaginal flushing with 200 mL of 0.2% chx diacetate every 6 h (200 mL sterile water control)	526 chx 521 Control	No difference in sepsis rates between the 2 groups (total 3 cases [2 in control, 1 in chx] RR = 0.50 [0.05, 5.45]). No difference in antibiotics administration, admissions to NICU, or mortality
Eriksen[32] (USA, 1997)	Randomized controlled trial	Impact of chx flushing on: Maternal peripartum infection; neonatal infections (sepsis, pneumonia)	Single vaginal flushing with 20 mL of 0.4% chx (20 mL sterile water control)	457 chx 453 Control	Only a single case of neonatal pneumonia (control group) and no cases of sepsis in either group; no difference in antibiotic treatment (RR = 1.65 [0.73−3.74])
Stray-Pederson[34] (Norway, 1999)	Randomized controlled trial	Impact of vaginal cleansing with chx on vertical transmission of GBS and subsequent neonatal infectious morbidity	120 mL of aqueous 0.2% chx flushing every 6 h (saline placebo control)	548 chx 582 Saline	Significantly less overall infectious neonatal morbidity (septicemia, respiratory problems, superficial infections-4.9% vs. 7.9%, $P < 0.05$); *Staphylococcus aureus* infections were also lower in chx group ($P < 0.01$)
Calkin[31] (UK, 1996)	Randomized controlled trial	Impact of vulval swabbing with chx on bacterial colonization of newborns, infections, and/or neonatal admissions	Vulva swabbed with 0.05% chx diacetate during labor and delivery (tap water control)	395 chx 416 Control	No difference in rate of neonatal admission to the special care baby unit ($P = 0.66$); colonization of infants for a variety of Gram-positive/negative bacteria equivalent
Developing countries (all hospital-based)					
Taha[4] (Malawi, 1997)			(See Table 4)		
Galliard[36] (Kenya, 2001)	Prospective clinical trial; alternating weeks with/without intervention	Impact of vaginal lavage with chx on mother-to-child transmission of HIV	120 mL of 0.2% (later increased to 0.4%) chx every 3 h (untreated comparison group)	HIV+ 309 chx 297 non-trt	No overall difference in rate of mother-to-child transmission; some evidence of reduced vertical transfer when lavage with 0.2% chx (OR = 0.6 [0.3−1.1]) or 0.4% chx (OR = 0.1 [0.0−0.9]) was done before rupture of membranes
Bakr[5*] (Egypt, 2005)			(See Table 4)		

* Intervention in these studies include both vaginal cleansing and neonatal full-body skin cleansing with chlorhexidine.

TABLE 4

Studies of the Impact of Neonatal Skin Cleansing With Chlorhexidine (chx) on Morbidity and Mortality in Neonates

Study	Design	Objective/Outcome(S)	Chlorhexidine Dose and Delivery Method	Sample Size	Results
Hospital-based studies					
Tuke[21] (UK, 1975)	Single-center prospective study; comparison of consecutive periods with and without chx bathing	Impact of chx full-body cleansing on overall incidence of superficial staphylococcal infections (eye, skin, umbilical)	Daily bathing with 10% dilution of Hibiscrub compared to previous period with nonantiseptic cleansing	~2000 chx ~2000 Control	Overall superficial infections were reduced among infants receiving chlorhexidine bathing (0.3% vs. 2.6%) (RR = 0.10 [0.04−0.25]
Meberg[50*] (Norway, 1985)	Randomized controlled trial	Impact of whole-body washing and umbilical cord cleansing with chx on superficial infections (eye, skin, umbilical)	4.0% chx Applied daily to the umbilical cord and entire body of infant until discharge (soap and water control group)	105 chx 111 Control	Superficial infections in the nursery were reduced (NS; RR = 0.35 [0.72 −1.70]). Overall 6-week superficial infection rate was 13% lower in the chx group (P = 0.75)
Taha[4†] (Malawi, 1997)	Prospective study; comparison of periods with/without/with intervention	Impact of chx cleansing (maternal and neonatal) on mother-to-child transmission of HIV and maternal and neonatal infections	Birth canal and external genitalia wiped with cotton soaked in 0.25% chx; every 4 h. Infant given single wipe with cotton soaked in 0.25% chx (untreated comparison group)	3743 chx 3417 non-trt	No reduction in vertical transfer of HIV; 12% (3%−21%) reduction in neonatal admissions to the NICU, 50% (24%−68%) reduction in neonatal sepsis, 50% (12%−71%) reduction in infection-related mortality; 22% (0%−40%) reduction in overall early neonatal mortality
Bakr[5†] (Egypt, 2005)	Prospective study; comparison of consecutive periods with and without intervention	Impact of chx cleansing (maternal and neonatal) on admissions to the NICU, overall neonatal morbidity, sepsis-related morbidity and mortality	Vaginal cleansing with cotton soaked in 0.25% chlorhexidine, followed by neonatal wipe with gauze soaked in 0.25% chlorhexidine (untreated comparison group)	2293 chx 2138 non-trt	Overall neonatal admissions rate was the same in both groups; infection-specific admission rate was reduced (0.7% vs 1.9%, P < 0.001); infection specific and all-cause mortality was reduced 75% (P < 0.01) and 33% (P = 0.01), respectively
Community-based studies					
Tielsch[6] (Nepal, 2005)	Cluster randomized, placebo-controlled, community-based trial	Impact of chx cleansing on neonatal mortality and morbidity	Single wipe with cloth impregnated with 0.25% chlorhexidine (placebo control group)	8519 chx 8787 Control	Overall neonatal mortality was 11% lower in the chx group (RR = 0.88 [0.72−1.10]). Among low-birth-weight infants, neonatal mortality was reduced 28% (5%−45%)

*Infants in the intervention group also received umbilical cord cleansing with 4.0% chlorhexidine.

†Intervention in these studies included both vaginal cleansing and neonatal full-body skin cleansing with chlorhexidine.

TABLE 5

Studies of the Impact of Umbilical Cord Cleansing With Chlorhexidine (chx) on Infection and Mortality in Neonates

Study	Design	Objective/Outcome(S)	Chlorhexidine Dose and Delivery Method	Sample Size	Results
Hospital-based studies					
Seeberg[61] (Sweden, 1984)	Two-site prospective study (A, B), comparing periods with and without intervention	Site A: Impact of chx cleansing of the cord on *S. aureus* superficial (eye, skin, umbilical) infections	4.0% chx Applied daily to the umbilical cord stump (dry cord care for retrospective controls)	2274 chx 580 Control	Overall incidence of *S. aureus* infections was reduced after initiating 4.0% chx cord cleansing (16.2% vs. 2.9%; RR = 0.18 [0.13−0.24])
		Site B: Impact of chx cleansing of the cord on omphalitis	4.0% chx Applied daily to the umbilical cord stump (70% ethanol for retrospective controls) (See Table 4)	1618 chx 1041 Control	Incidence of omphalitis in the nursery after initiating routine 4.0% chx cleansing was significantly lower (21% vs. 1%; RR = 0.04 [0.03−0.8])
Meberg[61*] (Norway, 1985)					
Belfrage[62] (Sweden, 1985)	Prospective study, comparing periods with and without intervention	Impact of daily cord cleansing with 4.0% chx on superficial infections (eye, skin, umbilical), and sepsis	4.0% chx Applied daily to the cord stump; daily 0.5% chlorhexidine in 70% ethanol (70% ethanol control group)	796 4.0% chx 164 0.5% chx 784 70% Ethanol	Pyoderma, paronychia, and omphalitis were reduced significantly (percent reductions: 58 ($P < 0.01$), 46 ($P < 0.01$), 100 ($P < 0.01$), respectively) in the 4.0% chx group compared to 70% ethanol; no reductions were seen in the 0.5% chx group; no difference in sepsis-specific rates was found between the 3 groups ($P = 0.294$)
Smales[63] (New Zealand, 1988)	Prospective cross-over study	Impact of daily cord cleansing with 4.0% chx on superficial infections (skin, eye, umbilical)	4.0% chx Applied daily to the cord stump until discharge; daily 10% Iodosan control group	234 chx 234 Iodosan	Incidence of superficial infection was reduced among infants receiving 4.0% chx (21% vs. 38%; RR = 0.55 [0.41−0.74])
Community-based studies					
Mullany[7] (Nepal, 2005)	Cluster-randomized, placebo-controlled, community-based trial	Impact of chx applications to the cord on omphalitis and neonatal mortality	4.0% chx Applications during the first 10 d of life (soap/water comparison, dry-cord-care controls)	4934 chx 5107 Soap 5082 Dry	Mild, moderate, and severe omphalitis was reduced significantly (32% [20%−42%], 54% [41%−64%], 75% [47%−88%] reductions, respectively). Overall neonatal mortality was reduced (RR = 0.76 [0.55−1.04]), and the impact was greater among infants enrolled within 24 h after birth (RR = 0.66 [0.46−0.95])

* Infants receiving 4.0% chlorhexidine solution also received 4.0% solution for full-body cleansing.