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Review of Omphalitis Interventions in India, Nepal and Pakistan Using Proximal, Intermediate and Distal Risk Factors

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REVIEW OF OMPHALITIS INTERVENTIONS IN INDIA, NEPAL AND PAKISTAN USING PROXIMAL, INTERMEDIATE AND DISTAL RISK FACTORS

By

Nina Natu Patel

August 24, 2015

INTRODUCTION: Four million infants die annually within the first 28 days of life (Mir, 2008). This first four weeks of life is known as the neonatal period, a time frame when infants are most vulnerable to disease and infection. Ninety-nine percent of neonatal deaths occur in low to middle income countries (Mir, 2008). A systemic infection known as sepsis is the ultimate cause of death in 36% of neonates (Mullany, 2006). Due to lack of population-wide surveillance in the developing world, the proportion of cases originating from umbilical cord infection is largely unknown. Researchers at Aga Khan University Hospital concluded in their community-based study that home births place neonates at risk for umbilical infection and sepsis. Home births are not sterilely performed and the resulting risk of infection is high (Karumbi et al., 2013). Sequelae of umbilical cord infections have been identified as necrotizing fasciitis and sepsis, which is a systemic infection that is often fatal. (Mir, 2008; Mullany 2007).

AIM: The aim of this study is to review proximal, intermediate and distal risk factors in order to determine which omphalitis interventions show the most promise.

METHODS: Community-based randomized trials in India, Nepal and Pakistan were reviewed to discern the proximal, intermediate and distal risk factors of omphalitis to determine whether a single or multi-level intervention would best address neonatal omphalitis.

RESULTS: A single intervention of 4% CHX has been displayed by numerous studies to effectively reduce the incidence of omphalitis-related mortality by approximately 25%.

DISCUSSION: Due to the high incidence of omphalitis among neonates, similarities in cultural practices surrounding childbirth, and existing study data, India, Pakistan and Nepal have been chosen as countries of interest. Proximally, agents of disease were identified and the etiologies of such pathogens were explored. Intermediately, delivery practices, hygiene of both caregiver and birthing attendant, the occurrence of skin-to-skin contact encountered by the newborn, cultural practices of applying unsanitary substances to the umbilical cord, and breastfeeding norms are analyzed. Distally, environment, ethnicity, socioeconomic status, health systems, and education levels are considered as determinants of this disease (Mullany, et al., 2006).

Numerous studies conducting community-based randomized trials have determined that implementation of the topical antiseptic 4% Chlorhexidine (CHX) can result in an approximate 25% reduction in overall neonate mortality and between a 27% to 54% reduction in the incidence of omphalitis (Imdad et al., 2013). Researcher also cited the long-standing safety record, low cost, strong adhesion rate and activity against both Gram positive and Gram negative bacteria as the reasoning behind the decision to choose CHX as the topical antiseptic (Mullany et al., 2006).

The United Nations Commission on Life-Saving Commodities for Women and Children have requested for the WHO to add 4% CHX to the list of essential medicines for children. The council is fast-tracking the registration of the medicine to promote manufacturers to produce the drug and drop the cost of it for commercial use. New training protocols for birth attendants will also include instruction on how to correctly apply the antiseptic. Continued stewardship of the CHX intervention could lead to a dramatic reduction in neonatal mortality in the rural regions of South-central Asia potentially saving the lives of over 450,000 newborns annually (Mullany et al., 2009).

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Author's Statement Page

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Aim of Study

The aim of this study is to review proximal, intermediate and distal risk factors in order to determine which omphalitis interventions show the most promise. Due to the high incidence of omphalitis among neonates, similarities in cultural practices surrounding childbirth, and existing study data, India, Pakistan and Nepal have been chosen as countries of interest. Cultural practices within these countries have confounded community-based research results in the past. This research report compiles risk factors in order to assist in discerning which prevention efforts are most culturally sensitive and effective.

Introduction

Background

Four million infants die annually within the first 28 days of life (Mir, 2008). This first four weeks of life is known as the neonatal period, a time frame when infants are most vulnerable to disease and infection. Ninety-nine percent of neonatal deaths occur in low to middle income countries (Mir, 2008). A systemic infection known as sepsis is the ultimate cause of death in 36% of neonates (Mullany, 2006). Due to lack of population-wide surveillance in the developing world, the proportion of cases originating from umbilical cord infection are largely unknown. Researchers at Aga Khan University Hospital concluded in their community-based study that home births place neonates at risk for umbilical infection and sepsis. Home births are not sterilely performed and the resulting risk of infection is high (Karumbi et al., 2013). Sequelae of

umbilical cord infections have been identified as necrotizing fasciitis and sepsis, which is a systemic infection that is often fatal. (Mir, 2008; Mullany 2007).

Exposure of the newly-cut umbilical cord to pathogens introduced through the instrument used for cutting, the caretaker, the birthing attendant or the environment can lead to localized infections that can lead to a fatal infections (WHO, 1996). Much of the lack of reporting is due to the commonality of home births, which are largely informal and performed by family members, community health workers, or traditional birthing attendants (TBAs), who do not capture and report data. Due to South-central Asia's cultural similarity surrounding home births and high incidence rate of neonatal deaths stemming from unclean cord practices, India, Pakistan and Nepal will be the focus of this research report.

Epidemiology

An infection of the umbilical cord is medically termed *Omphalitis* (Mir, 2008). Omphalitis can initially presents as superficial cellulitis which can quickly spread to the abdominal wall. As it progresses, the infection can develop into necrotizing fasciitis and later into sepsis, which is often fatal for infants without access to antibiotics. The highest proportions of neonatal deaths occur in South-central Asia and sub-Saharan Africa, where a number of determinants increase the risk of this disease (Lawn, 2005). Interestingly, most epidemiological studies often focus on the 1% of neonatal omphalitis that occurs in more affluent, developed countries (Lawn, 2005; Mir, 2008**).**

Omphalitis is not a major risk in industrialized nations, where aseptic hospital births are the norm (Mullany et al, 2013). According to MedScape, the incidence of omphalitis occurs in

industrialized countries within less than .07% of the neonate population compared to as high as 20% in rural regions of non-industrialized nations (Gallagher, 2014). This disease remains to be a predominant agent of neonatal mortality in resource-poor developing countries, where home births are commonplace. The urgency of this issue has been identified by the United Nation's Millennium Development Goals, whose efforts to reduce child mortality created protocols for educating TBAs on preventing omphalitis. Future goals focus on this critical neonate period as the area for most improvement in regard to reducing child mortality below the age of five (United Nations, 2014).

A medical textbook of Pediatric Medicine reports the global incidence of omphalitis as determined by hospital-based studies range from 2 to 54 per 1000 live births (Ameh, 2008). This data is gathered from hospital-based public health surveillance, which does not apply to areas most burdened by neonatal sepsis, such as South-central Asia and Africa. The wide range in incidence highlights the disparity in health, but community-based studies in rural Pakistan further elucidate this disparity by reporting rates as high at 217 per 1000 live births (Ameh, 2008). This increased risk of disease in is further demonstrated by a number of community- and hospital-based studies conducted regionally in South-central Asia.

One study conducted by the Johns Hopkins Bloomberg School of Public Health sought to identify risk factors and incidence rates in Southern Nepal. The study found that omphalitis was present in 5.5% of the cohort of 17,000 newborns (Mullany et al., 2006). Another community-based cohort study in Pakistan found that omphalitis was identified in 21.7% of live births in home settings. Of these, 170 per 1000 were categorized as moderate to severe (Memon, 2013). This category of infection requires that the disease to have progressed to cellular or necrotizing

fasciitis, sepsis, or death. To further display the correlation between home births and omphalitis, a study in India compared the incidence of omphalitis in hospital births and home births. The study found that omphalitis was present in 2.3% of hospital births; whereas, home births resulted in nearly 10 times the number of cases at 21.3% (Faridi, 1993).

These studies have identified a common link among the high incidence rate of omphalitis: Home Births. Unfortunately, health systems in rural areas of India, Pakistan and Nepal do not allow for the entire population to have access to hospital births. Furthermore, the cultural practices of home births have been long established and are both culturally and religiously sensitive to the mores of local communities.

The disparity of the incidence of omphalitis between hospital and home births cannot rely soley on the development of mass health systems infrastructure to increase access to hospital births. For many women in rural areas of the developing world, health facilities require prohibitively long travel (WHO, 2009). In order to achieve post-2015 Millennium Development Goals, the focus must instead be on pragmatic, low-cost interventions that can be implemented through capacity building and education (WHO, 2009).

The World Health Organization's Statistics report in 2012 displayed the stagnant state of neonatal infections, which remained the same between 2000 and 2010 in India and Pakistan and increased by 1% in Nepal (WHO Statics Report 2012, 2012). This ten year period of no marked improvement on sepsis reduction provides evidence of the lack of reach public health efforts are having on rural home births, which comprise more than 50% all of the births in these countries. In fact, a number of researchers have explicitly stated the shortfalls of health care

outreach in rural areas is poor (Bamji, et al., 2008; Bhutta et al, 2011; Mullany, et al., 2009). In order to fully understand this disease and the interventions that would results in the greatest outcomes, it is imperative to identify the risk factors and determinants of disease associated with it that are regionally specific.

Determinants & Risk Factors

A comprehensive study conducted by Mullany et al. (2006) in Southern Nepal in order to identify what previous researchers neglected to, which was to determine the specific risk factors associated with omphalitis in home birth settings. These researchers identified proximate, intermediate and distal determinants of omphalitis. Proximally, agents of disease were identified and the etiologies of such pathogens were explored. Intermediately, delivery practices, hygiene of both caregiver and birthing attendant, the occurrence of skin-to-skin contact encountered by the newborn, cultural practices of applying substances to the umbilical cord, and breastfeeding norms are analyzed. Distally, environment, ethnicity, socioeconomic status, health systems, and education levels are considered as determinants of this disease (Mullany, et al., 2006).

Proximal Risk Factors

Proximally, this disease is caused by the colonization of bacteria on the highly vascularized and newly-cut umbilicus of a newborn, which can quickly spread to the surrounding soft tissue or into the bloodstream causing septicemia. Understanding the origin of these pathogens could provide insight into prevention for exposure to these microbes. Unfortunately, data on the etiologic pathogen of infection in low-income, rural settings where home births prevail is scarce

(Ganatra & Zaidi, 2010). Much of the data that exists is based on hospital data, which is not necessarily transferrable to the community-based setting. One hospital-based study conducted by Faridi et al. (1993) in India found Gram negative bacteria, specifically *Klebsiella spp*., to comprise more than half of the bacteria cultured from the infected umbilicus of neonates. The second most commonly cultured bacteria were found to be *Staphylococcus aureus* (Faridi et al., 1993). In contrast, a more recent community-based study conducted by Mir et al. (2011) in Karachi, Pakistan found 82% of pathogens to be Gram positive with *S. aureas* found in 52% of these cases. Gram negative bacteria were found in 18% of the cases with *Pseudomonas spp* comprising 9% of those cases and *Klebsiella spp* posing the lowest risk (Mir et al., 2011). These two studies display a varying clinical picture of omphalitis with hospital-based etiology in India predominantly Gram negative and community-based etiology in Pakistan as Gram positive. The importance of understanding the most common agents of disease comes when pairing topical antiseptic interventions with neonates in different regions. Either the topical intervention must work equally well at addressing Gram positive and Gram negative bacteria, or more specific interventions must be created.

A study conducted by Ganatra & Zaidi (2010) explored the microbial etiology of neonatal sepsis in developing countries by regions, including South Asia. Only five studies were community-based and all found *Klebsiella spp.* as the predominant microbe in 25% cases, but most infections were considered to be polymicrobial. *S aureas* and E. coli were responsible for 9.86% and 12.05% of the cases in South Asia, respectively. These three organisms are responsible for 44% of the etiology of neonatal sepsis worldwide. Researchers reported that South Asia data displayed *Klebsiella* to be most highly identified agent in cultures. Due to the

limited data available for researchers due to the commonality of home births, considerably more needs to be done to fully understand the true etiology of disease in South Asia. In Nepal, few etiological studies have been conducted as resources in that region are needed to conduct such research.

Intermediate Risk Factors

Intermediate factors play an integral role in the increased risk of neonates in the South-central Asian region. One of the greatest distinctions between countries with this disease burden is the prevalence of unsanitary home births, which are estimated at more than 80% in rural areas of South Asia (Ganatra & Zaidi, 2010). This issue is often coupled with a lack of antenatal care and access to a skilled health worker during delivery. This lack of access to educated health workers can perpetuate unsafe practices, such as dirt floor deliveries, unsterile cord cutting, unsafe applications to the umbilical cord and delays in breast feeding (Ganatra & Zaidi, 2010).

Discouragement of skin-to-skin contact between the mother and newborn and delayed breast feeding can further compromise the immune response to such pathogens. Following childbirth, mothers are viewed as being both physically and spiritually unclean in a rural region of Karnataka, India (Kesterton & Cleland, 2009). This belief was also echoed in Nepal and Pakistan, where the delay was attributed to the need for a new mother to rest fully and bathe (Mullany et al., 2013; Imdad et al., 2013). In Nepal, mothers are discouraged from holding their newborn following birth and promoted by elders to bath fully before they engage in skin to skin contact with their newborn. Interestingly, this initial contact promotes the colonization of

protective skin flora and was associated with a 36% decrease in risk of infection in Nepal (Mullany et al., 2013). Contrary to research, traditional practices of home births often result in preventing the mother from having skin-to-skin contact for up to 2 days. Additionally, newborns are often bathed so as to remove the vernix layer, the greasy protective coating, which is also thought to be make the baby look unclean (Kesterton & Cleland, 2009). Fikree et al (2005) reported similar findings regarding discouragement of immediate skin-to-skin contact between mother and child. Numerous researchers have determined that skin-to-skin contact between mother and newborn can initiate colonization of beneficial skin flora that can be protective to the neonate (Mullany, et al., 2006; Lawn et al., 2006). These common traditions in India, Nepal and Pakistan are eclipsing the importance of these initial interactions between mother and child that researchers believe to be protective against infections and decrease risk of omphalitis in home birth environments. The need for education among community health providers and new mothers is needed to assure that the benefit of these behaviors is understood and the discouragement of such practices ceases.

The delay in mother-infant contact is viewed as a time for the mother to both rest and cleanse herself (Bhutta et al, 2011). Unfortunately, the delay only leads to further deviation from what is considered best practices for newborns, which the WHO believe to be only providing newborns with breast milk when possible (WHO, 2009). Colostrum, the initial viscous and yellow-colored expression of lactation is in many areas of South-central Asia thought to *not* be nutritive (Bhutta et al, 2011). In India, researchers found that sugar water is sometimes given to newborns during the first 2-4 days of birth due to the delay in mother to infant contact (Ashwini et al, 2014). The administration of sugar water as a pre-lacteal feed in 20% of the

population of rural Karnataka of which 80% of the home births were conducted by neighbors or relatives who have had children (Kesterton & Cleland, 2009). This practice originated from government protocol training in the late 1990s for community health workers working in rural areas. Although the practice was later discouraged and health workers were retrained on the benefits of breast milk-only diets, many non-health workers continue this practice when assisting family and neighbors in childbirth (Kesterton & Cleland, 2009). Similarly, researchers in Pakistan has also reported nearly 31% of mothers delay first feed and 55% report giving prelacteal feeds, such as *ghutti* or honey (Fikree et al., 2005). In Nepal,

A cross-sectional study in Belgaum, India conducted by the International Journal for Public Health and Medicine authored by Ashwini, Katti and Mallapur (2014) found similar to previous studies that 57% of newborns were given pre-lacteal feeds that were primarily honey and water. Twenty-five percent of the study population discarded colostrum. A number of international studies found that in all the Indian states, rates of exclusive breast-feeding were between 10% and 61%. Ashwini, Katti and Mallapur (2014) determined that 65% of mothers were lead to delay lacteal feeding and to discard colostrum on the advice of their elders. This study concluded the importance of including elders on education and training in rural communities to assure that best practices are relayed to and stewarded by those ultimately guiding such decisions.

Kesterton & Cleland (2009) conducted in-depth qualitative interviews in their study based in Karnataka, India to identify the origin and impetus for non-science-based beliefs and behaviors. Results showed that mothers were advised by health workers and informally trained female birthing attendants (known as Dais) but final decisions were almost exclusively made by

the paternal grandmother. The beliefs held by the grandmother are often grounded in religion, superstition and tradition and are often contrary to widely regarded notions of infection and transmission. One particularly alarming convention was one that women are asked to give birth in a cowshed so as to not "pollute" the home. When one interviewer asked, "Could you do the delivery somewhere cleaner, in the house rather than the cowshed?", the grandmother responded, "Yeah, yeah will you come and clean out all the blood? I am not going to do it in the house. God is inside the house and delivery is polluting, so I can't do it in the house" (Kesterton & Cleland, 2009). In order to best solve the issue of neonatal infection, harmful practices in place must be identified and muted. Other intermediate factors related to omphalitis were predominantly linked back to the instrument used to cut the umbilical cord, and hygiene practices of the birthing attendant and the caregiver (Mullany et al, 2009; Karumbi, et al, 2013).

Common avenues for introducing bacterium include cultural practices of applying dung, clay, ash, fluid from pumpkin flowers, ghee, mustard oil, powder ground from tree bark and saliva to the umbilical cord (Karumbi, et al, 2013). The application of ghee correlated with tetanus in a number of studies (Karumbi, et al.,2013, Bamji, et al., 2008). In Mullany et al.'s Nepalese study, ash and mud were not implicated directly with infection (Mullany et al., 2006); however, these substances have been associated with risk of neonatal tetanus in previous studies in Karachi, Pakistan (Mir, 2008). According to Mullany et al., mustard oil was applied to 80% of the neonate cohort of 23,246 and also had the highest statistical association with infection in Nepal.

Another study conducted by Mullany et al (2007) in the Sarlahi district of Southern Nepal found that the practice of massaging a newborn with mustard oil occurred in 99.7% of the

8,537 cohort, which was considered to be “overwhelmingly prevalent.” Interestingly, this behavior was found to occur independent of ethnicity, religion, socioeconomic status or cultural differences. Although the practice is considered to be detrimental to a child’s health due to the unknown quality of the substance and potential for being a bacterial reservoir, little has been concluded of the evidence-based harms and benefits of the application (Mullany et al., 2006). Currently, the only evidence found to definitely display harm caused by the application of mustard oil was published by Darmstadt et al (2002) in their India-based study, which determined that the practice “has toxic effects on the epidermal barrier that warrant future investigation”. Continued research is clearly needed to determine if mustard oil is contributing to the cause of disease in addition to the current evidence of statistical association with omphalitis.

S. aureus was most commonly introduced from the hands of the caregiver and birthing attendant, which were reported as not having been sanitized following a home birth by the majority of study participants (Bhutta, 2010). The instrument used to cut the umbilical cord was most often found to introduce tetanus to the neonate, resulting in tetanus neonatorum, which also presents as a local infection of the umbilical cord. In India, diligent hand washing and sanitization following birth of both the caregiver and the birthing attendant was scarcely reported (Bhutta, 2010). In Nepal, Mullany et al.’s (2007) study demonstrated that hand washing with soap and water by the birthing attendant prior to delivery as well as by the mother for the following 14 days was protective to the newborn.

Although this practice of diligent hand washing is commonplace among the Western world’s medical protocol, this practice is not a staple of rural regions of South-central Asia. It is

imperative to understand disparities and the feasibility of implementation. During a trip to Nepal in 2012, I was utterly baffled by the limitations of access to water and my ability to practice what I considered basic hygiene in deeply poor and rural areas that experience these "easily solvable" health disparities. In regions rural regions of South central-Asia, women are sent to gather a bucket or two of water daily from a nearby stream or well primarily for the purposes of cooking and bathing. Many people in these rural areas bathe with less than one gallon of water. Although it is simple to say, "wash your hands before you touch your newborn," the practicality of that request is contingent upon that individuals access to clean water.

Distal Risk Factors

Distal factors including the level of education of the caregiver, the level of training by the birthing attendant and environments were found to have the most correlation of risk or protective benefit with infection. Mothers with the highest level of education were found to have better health outcomes in India (Kesterton & Cleland, 2009). Birthing attendants' level of training was found to be comparable, but it was noted that diligent hand-washing was not an institutionalized practices prior to delivery in the study location of Karnataka. Infection was also more prevalent during the hottest months of the year. Ethnicity and the level of paternal education was not found to have any association with risk of infection (Kesterton & Cleland, 2009). In Karachi, Pakistan, Fikree et al (2005) found that the education level of the mother was not correlated with health outcomes of newborns. Interestingly, even with all of the ethnic and religious differences in this region of Pakistan, many of the traditions surrounding childbirth are ubiquitous resulting in similar health outcomes (Fikree et al., 2005).

A study by Lawn et al (2010) focusing on worldwide risk factors found that there were three major delays that could be bridged through health worker and maternal education to reduce neonate mortality. These delays were in: 1.) recognizing a problem and understanding when it is time to seek care, 2.) delays in reaching a health facility, and 3.) delays in receiving a good quality of care. Researchers determined that the best way to amend for these lapses were education of community health workers and mothers (Lawn et al., 2010). These issues are all linked to education and strengthening health systems. Home births may be the prevailing method of delivery, but there are ways of assuring that mother and health workers understand when a health issue needs to be addressed by a physician or specialist. Although facilities may be difficult to reach, a plan for reaching such care could be made prior to any issues arising. Finally, it is necessary for providers to assure that mothers and neonates receive a high quality of care that focuses on educating mothers and caretakers to allow for the dissemination of information back to rural areas.

Other factors, such as the separation time of the cord are also vital to the determination of most effective interventions. The cord is the primary vulnerable site for infection on a neonate, therefore, reducing the cord separation time directly decreases the risk of cord infection. Being that clinical presentation of omphalitis takes place between 5-9 days for full gestation births and 3-7 days for pre-term births, the necessity to incorporate a shortened cord separation period is prudent.

Proximal, Intermediate and Distal Risk Factors Associated with Omphalitis in Pakistan, India and Nepal			
Study	**Proximal**	**Intermediate**	**Distal**
Faridi et al., 1993	Klebsiella *spp* S. *aureas*	Discouragement of skin-to-skin contact Removal of vernix layer through bathing	Level of education Education level of caregiver
Mullany et al., 2013	Pseudomonas *spp*	Delay in breastfeeding	Level of training by attendant
Mir et al., 2011		Discarding colostrum	Environmental factors
Kesterton & Cleland, 2009		Administration of sugar water as pre-lacteal feed	Long umbilical cord separation time
Mullany et al., 2013		Superstitions and traditions surrounding childbirth	
Karumbi, et al, 2013		Delivery in unclean areas outside of the home	
Bamji, et al., 2008		Unclean cutting instrument	
Mullany et al., 2006		Practice of applying dung, clay, ash, fluid from pumpkin flowers, ghee, mustard oil, powder from tree bark and/or saliva to the umbilical cord	
Mir, 2008		Massaging newborn with mustard oil	
		Lack of hand washing	
		Non-sterile home births	
Mullany et al., 2013 Mullany et al., 2006 Bhutta, 2010			

Interventions

A number of past studies focusing specifically on omphalitis have focused on antiseptic application to the newly cut umbilical cord. Due to the complex nature of the issue of omphalitis, it is difficult to understand what interventions will have the most beneficial outcome due to the cofounding risk factors. In order to assess which interventions might be the

more effective, single facet (i.e. antiseptic application) and multi-level (i.e. health worker training, education and birthing kit) intervention approaches will be discussed. Conclusions will then be reviewed as to determine their feasibility and impact based upon the proximal, intermediate and distal risk factors previously identified. The incidence of neonatal infections in low-income, resource-poor regions of Nepal, India and Pakistan will guide the review of interventions assuring they consider the resources available, the cultural and behavioral risk factors, as well as the known agents of disease.

Chlorhexadine 4% Intervention

Application of topical antiseptic to the umbilical cord has been promoted above dry cord care by the WHO in areas where risk for infection is high (Capurro, 2004). A number of studies in the early 2000s were conducted comparing various topical antiseptics, including alcohol, chlorhexadine (CHX), triple dye, and povidone iodine, but data was inconclusive as to whether any topical antiseptic shows marked improvement compared to dry cord care (Zupan, Garner & Omari, 2004). Many of the practices identified as potential risk factors, such as the common practices of oil massage and applications of foreign substances to the umbilical cord may have confounded early results.

In 2006, research conducted by the Nepal Nutrition Intervention Project between 2002 and 2005 determined that CHX was the most favorable topical antiseptic choice when compared to ethanol, silver sulfadiazine, triple dye, gentian violet and povidone iodine (Mullany et al., 2006). Researchers cited the long-standing safety record, low cost, strong adhesion rate and activity against both Gram positive and Gram negative bacteria as the reasoning behind the

decision to choose CHX as the topical antiseptic for trial (Mullany et al., 2006). This double-masked, placebo-controlled, community-based trial enrolled 15,123 newborn babies into 4% CHX umbilical applications, soap and water or dry cord education only. All families were provided clean delivery kits and were used in 97.8% of households, which provided a clean cutting tool and sanitary items for labor. The randomization groups were stratified and standardized by caste, ethnic group, electricity, radio/television access, maternal literacy, and delivery place. These distal factors were not found to have any impact on the incidence of omphalitis among the cohorts. Soap and water and dry cord care interventions showed no significant reduction in the incidence of omphalitis with a rate of 15.7 and 15.2, respectively. Among the CHX group, the rate of omphalitis was reduced to 10.3. The results displayed that CHX could reduce the risk of cord infection by 32-75% and reduce risk of mortality by up to 24% (Mullany et al., 2006).

More recent community-based studies conducted in Nepal with the support of The Bill and Melinda Gates Foundation have also ostensibly determined that CHX use can reduce neonatal mortality by up to 24% and has had the fewest side effects when compared to other antiseptics (Mullany et al., 2009). These studies have created a large body of evidence of the benefits 4% CHX umbilical cord cleansing for surrounding countries to use as a model for their own intervention strategies. Interestingly, although *all* families were educated to not apply any foreign substances to the umbilical cord, the dry cord care group reported applying mustard oil at 54%, which was 7.5% more often than soap and water and CHX groups. This difference between the groups may be a glimpse into the predisposition of families to apply *something* to

the umbilical cord. This is a paradigm shift for practices in the Western world, where dry cord care is the norm.

Imdad et al. (2013) conducted a meta-analysis published in *BMC Public Health* that focused on 4% CHX topical antiseptic vs. dry cord care in cluster randomized community-based trials in Nepal, Bangladesh and Pakistan. The analysis included data from 54,624 neonates receiving at least one application of CHX within 1 to 10 days of birth. Results indicated that there was a 24% reduction in overall neonate mortality and between a 27% to 54% reduction in the incidence of omphalitis (Imdad et al., 2013). These results further indicate that the application of CHX can be an effective intervention in the prevention of omphalitis in this region of Asia. Interestingly, cord separation time was longer in the cohort treated with CHX than the control, but there was no increased risk of infection (Imdad et al., 2013).

Cholarhexadine 4% Paired with Handwashing Intervention

Another study conducted by Soofi et al (2012) in Pakistan sought to research three treatment arms and dry cord care as a control group. The treatments included CHX application alone, hand washing alone, and CHX combined with hand washing. The findings were published in *The Lancet* and determined that hand washing implemented by the birthing attendant and caretaker had no protective effects against omphalitis alone. Furthermore, no additional protection was gleaned from the combination of CHX and hand washing in tandem. Meaning, CHX was found to be equally protective against omphalitis when paired with or without hand washing. Researchers concluded that CHX should become a staple in birthing kits and distributed through the existing networks of health workers to increase reach and access to the

intervention in addition to the continued efforts in health systems strengthening (Soofi et al., 2012). Most importantly, this study highlight the effectiveness of a single intervention as capable of reducing neonate mortality. Due to the complex nature of this disease and the numerous cultural and behavioral adverse health behaviors that persists, the effectivity of a single intervention is essential for broad implementation. Numerous studies have determined the protective benefits of CHX application, but these interventions are most pressing in poor and rural villages. It is necessary to determine the availability of the topical antiseptic for those who do not have access to a skilled birthing attendant who may provide the application or funds to procure it.

Chlorhexadine 4% Feasability for Poor Households

With regard to access to CHX, one study determined that the willingness for growing households to pay for CHX was approximately 30% for products priced at current market value. All respondents in the study were willing to pay *some* amount for the product but prohibitive factors were linked to cost (Coffey et al., 2013). Although CHX has significant data supporting it effectiveness to treat this disease, it is difficult to discern if access to this antiseptic is feasible as it would not be commonly found in the home. Due to this potential barrier to receive the medication, it is necessary to either subsidize this substance to improve access or determine equally effective alternatives. Breast milk, for instance, is a resource that is available to new mothers' and has been found to have immunological compounds that increase the rate of cord separation and also contains natural antiseptic properties (Aghamohammadi, Zafari & Moslemi, 2012).

Topical Breast Milk Intervention

One such topical breast milk study conducted in Iran found that separation time was significantly decreased with the administration of breast milk in comparison to povidone iodine, 7.7 and 9.7 days respectively (Vural & Kiza, 2006). Amirfarhani et al. (2008) reported in their study comparing breast milk to dry cord care that the bacterial colonization in breast milk cohorts was slower and bacteria cultured were less pathogenic. This study identified dry cord care bacteria to predominantly be *Staphylococcus aureus, E. coli and Klebsiella spp.,* whereas the breast milk cohort was found to have *Staphylococcus epidermidis,* which is less aggressive and leads to fewer severe cases of omphalitis *(*Amirfarhani et al., 2008).

Two other breast milk application studies conducted by Golshan & Hossein (2013) and Pujar et al (2013) in India and Pakistan published similar results indicating that breast milk applications were correlative with a significant decrease in cord separation time when compared with alcohol and/or dry cord care. These studies, however, did not find a significant difference in the incidence of omphalitis among the treatment arms (Golshan & Hossein, 2013; Pujar et al, 2013). Breast milk may be a promising treatment for areas of South central-Asia where antiseptics are not available as it has been found to significantly reduce the cord separation time and slow colonization rates of bacteria. In order to better understand the protective effects of this treatment, a multi-center study must be performed to to verify if incidence rates of omphalitis reduced compared to other feasible treatments.

Multi-level Birthing Kit Intervention with CHX 4%

Along with interventions that focus on promoting antiseptic use on the umbilical cord, birthing kit interventions promote the "three cleans" have been promoted in developing countries where home births are common by the WHO. These components include a clean delivery surface, clean cutting instrument, and clean hands of the birthing attendant. A meta-analysis performed by Vanora et al. (2012) published in *Midwifery* reviewed interventions taking place in the subcontinent of Asia. The respective birthing kits analyzed to determine what may become best practices for birthing kit contents. The kits varied in contents ranging from a plastic sheet, soap, a clean blade, a cord or umbilical clamp, a form of cord care (including clean gauze or antiseptic), pictorial instructions and disposable gloves. Results showed that this intervention reduced the incidence of neonatal tetanus as a result of the inclusion of a clean cord cutting instrument. Furthermore, incidence of neonatal mortality was reduced along with maternal sepsis. Although the birthing kit is designed to be disposed of after use, the study found that many women were reluctant to dispose of the birthing kit following use. The study concluded that no single intervention strategy was going to handle the complex issues of maternal and child health in these regions. Instead, a more sophisticated, multi-level approach incorporation education and capacity building would be required (Hundley et al. 2012). Birth kit interventions focus on the intermediate risk factors and seek to increase the cleanliness of the birthing process in order to prevent child and maternal infection. Unfortunately, these interventions do not account for the potentially confounding behaviors practiced by women in the region that may override any antisepsis efforts during childbirth.

Multi-level interventions inclusive of education along with birthing kits may also serve as insight into standard of care for newborn and maternal care as health systems strengthen and

capacity building among health workers increases. One such pilot study conducted by Bhutta et al (2008) in India and published in the Bulletin of the World Health Organization as an applicable intervention for South Asia as a whole sought to improve education and training on best-practices for newborn care. The study focused on two levels of education for the existing network of government-trained Lady Health Workers (LHW), local Dais (informally trained birthing attendants), and the villages in which they serve. In the intervention villages, the LHWs were trained in perinatal care, which included promotion of antenatal care, folate use, immediate newborn care, cord care and promotion of breastfeeding exclusively and within the first hour. Cord care involved training on avoiding use of potentially harmful substances such as mustard oil, ash and powders. The trained LHWs would then go on to train local Dais and lead group session education in the communities with stakeholders, such as adolescents, women of reproductive age, and female elders. Additionally, the Dais were provided birthing kits with methods of sanitarily cutting the umbilical cord as well as sanitizing hands before and after the birthing process (Bhutta et al., 2008).

Results from the pilot study displayed a marked decrease in early and late neonatal mortality, approximately 19% and 49% respectively (Bhutta et al., 2008). Although this intervention was not designed to specifically research omphalitis, many of the intervention strategies directly address the risk factors that have been identified with the disease. Total neonatal mortality was 27.8% lower than baseline data established in previous study control groups (Bhutta et al., 2008). The overall impact of a multi-level approach clearly displays an improvement in neonatal health outcomes which peripherally implies that this intervention is also decreasing the rates of omphalitis. Most importantly, this intervention implements

evidence-based protective behaviors and mutes a number of adverse health behaviors leading to the overall improvement in the health of neonates. Interestingly, education on cessation of applications to the umbilical cord, training on ideal bathing practices, and providing a clean cutting instrument were the only interventions directly targeted at omphalitis prevention. Health workers were not provided with any antiseptic for application to the umbilical cord.

This intervention strategy honed in on a multi-level approach targeting intermediate and distal risk factors, including education to caretakers and health workers on current best practices. The discouragement of placing potentially harmful substances on the neonate may prevent the proximal risk factors of bacterial colonization that could lead to omphalitis. Additionally, the promotion of immediate and exclusive breast feeding may promote immune development and colonization of health skin flora that may be protective to the neonate. This style of intervention primarily focuses on education rather than physical resources, which makes it an ideal long-term strategy for resource poor regions of Pakistan, India and Nepal. Unfortunately, the health systems strengthening efforts would require time to coordinate and may leave thousands of neonates at risk in the interim.

Discussion & Conclusion

Discussion

Due to the increased incidence of neonatal infections in low-income, resource-poor countries, such as India, Pakistan and Nepal, it is important to design interventions that are sensitive to the resources available, the cultural and behavioral risk factors and the agents of disease. As discussed, a multi-level approach that incorporates health worker training, family

education and birthing kits are ideal, but the resources needed would require significant health systems strengthening. Birthing kits show promise for both neonate and maternal outcomes, but the lack of post-natal antisepsis instruction with regard to neonates leaves them open to infection following traditional practices of mustard oil massage or foreign substances placed on to the umbilical cord. These kits can equip health workers with a few very important items to lower the risk of neonatal infection: soap for assuring that delivery in as sanitary as possible, a clean umbilical cord cutting instrument and 4% CHX for the newly cut umbilical cord and extra for parental application.

Although breast milk interventions may be best for extremely resource-poor regions with no access to antiseptics, the evidence of the benefits of topical CHX are the most undeniably effective single intermediate level intervention for neonate mortality reduction, according to the body of research in the subject matter. One document prepared for the United Nations Commission on Life-Saving Commodities for Women and Children have requested for the WHO to add 4% CHX to the list of essential medicines for children. Furthermore, the council is fast-tracking the registration of the medicine to promote manufacturers to produce the drug and drop the cost of it for commercial use. New training protocols for birth attendants will also include instruction on how to correctly apply the antiseptic. These recommendations are designed to address the portion of neonatal deaths that originate from umbilical cord infection in South Asia and West Africa and could save over half a million lives annually (Segre et al., 2012).

Study Limitations

More studies that focus on reducing the dangerous cultural behaviors are needed to assure that antiseptic interventions are not confounded with non-sterile applications, such as mustard oil and ash. Studies that focus on reducing these behaviors could, ultimately, reduce the incidence of disease due to the contamination inherent in substances being applied to the umbilical cord. More educational intervention that focus on educating mothers and community elders are needed to assure information regarding best practices is disseminated. Research is also needed to address what access families have in the instance of infection or disease among a neonate.

Conclusion

The cost for these interventions is relatively low and the impact is remarkably high. Thousands of newborns could be saved through CHX interventions alone. When it comes to the need for continued promotion of high-impact interventions to improve neonatal survival, the potential for CHX to save lives is evident. The public health benefit would be substantial for those programs whose goals are to focus on child morbidity and mortality reduction. Widespread implementation of simple antiseptic interventions for all home born babies, a marked acceleration in the reductions in neonatal mortality could propel South central-Asia toward Millennium Development Goals.

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