Efficacy of chlorhexidine application to umbilical cord on neonatal mortality in Pemba, Tanzania: a community-based randomised controlled trial

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Summary

Background In low-income countries, including the east African region, a third of neonatal deaths are due to infections. A substantial proportion of these have been attributed to sepsis, which can result from umbilical cord infections. Evidence from Asia suggests that chlorhexidine application to the neonatal umbilical cord reduces mortality, but no data from Africa are available. We aimed to assess the effect of umbilical cord cleansing with 4% chlorhexidine solution on neonatal mortality and omphalitis in rural settings of sub-Saharan Africa.

Methods We did a community-based randomised controlled trial on Pemba Island, Zanzibar, Tanzania. All eligible babies (aged 1 h to 48 h, without congenital malformations) from hospital-based and community-based deliveries on Pemba Island were enrolled. Participants were randomly assigned to either 4% free chlorhexidine for cord care or to dry cord care using a computer-generated random sequence. For babies allocated to the chlorhexidine group, mothers or caretakers were advised to apply the solution to the cord every day until 3 days after the cord had dropped off. Cord stumps were examined for redness, pus, swelling, and foul odour on day 0, 1, 4, 10, and 28. The primary outcome for this study was mortality until day 28 on an intention-to-treat basis. The trial is registered with ClinicalTrials.gov, number NCT01528852.

Findings Between May 19, 2011, and Aug 31, 2014, 36 911 newborn babies were enrolled into the chlorhexidine (n=18 015) and dry cord care study (n=18 896) groups. 17 468 (96·9%) of 18 015 neonates in the chlorhexidine group were available for complete follow-up (28 days) compared with 18 384 (97·3%) of 18 896 neonates in the dry cord care group. Mortality rate in the chlorhexidine group (10·5 deaths per 1000 livebirths) was not significantly lower than that in the dry cord care group (11·7 per 1000 livebirths; relative risk 0·90, 0·74–1·09; p=0·27).

Interpretation Our findings do not support the use of chlorhexidine for reduction of neonatal mortality in this east African setting, which might not justify a change in the WHO policy. To inform global policy, a detailed meta-analysis and pooled analysis needs to be undertaken using data from both African and Asian settings.

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Introduction

Asia and sub-Saharan Africa have the highest neonatal mortality rates in the world (about 29 deaths per 1000 livebirths),[1] with about 50% of neonatal deaths occurring on the first day of life.[2] Although post-neonatal mortality rates have reduced substantially over the past 25 years, deaths in the neonatal period have decreased more slowly and now account for 47% of all deaths in children younger than 5 years.[1] The worldwide neonatal mortality rate fell from 36 deaths (95% CI 35–38) per 1000 livebirths in 1990 to 19 (95% CI 18–21) in 2015.[1] Infections are estimated to be responsible for 31·5% of these deaths between 2000 and 2015.[3,4] Neonatal sepsis affects six to 21 babies per 1000 livebirths, with a case-fatality rate of 27–56% leading to more than 336 357 deaths per year.[3] Percutaneous invasion of pathogens from umbilical cord infections has been postulated as a major cause of neonatal sepsis.[5,6]

Unsanitary conditions in delivery and care of newborn babies might contribute to the high rate of omphalitis and serious systemic infection.[7] Approaches such as hygiene promotion (including handwashing related to delivery and neonatal care), intrapartum vaginal and neonate skin cleansing with antiseptics such as chlorhexidine, and use of clean birth kits have been implemented to reduce the risk of neonatal infections.[8–10] Three clinical trials[7,8,11] have provided evidence about the effectiveness of chlorhexidine application to the neonatal umbilical cord in Asia, but no data from Africa exists. Current WHO guidelines[12] suggest application of chlorhexidine to the umbilical stump during the first week of life for babies born at home in settings with high neonatal mortality (≥30 neonatal deaths per 1000 livebirths) and to use dry cord care for newborn babies in settings with lower (<30 deaths per 1000 livebirths) neonatal mortality.

Chlorhexidine, a broad-spectrum topical antiseptic with strong residual activity, has been shown to be

Research in context

Evidence before this study

We searched PubMed and the Cochrane Library with search terms "chlorhexidine", "cord care", "mortality", and "omphalitis" for all articles published in English until November, 2015. Three trials from southeast Asia (Nepal, Bangladesh, and Pakistan) have reported the effects of chlorhexidine on neonatal mortality and omphalitis. They reported significant effects of chlorhexidine on reducing neonatal mortality, but some questions remain unanswered. The study in Bangladesh showed an effect of 1 day treatment of chlorhexidine, but no effect was observed with 7 day treatment; the study in Nepal was not statistically significant for overall effect; and the study in Pakistan presented a factorial analysis with a clinically important interaction (maternal handwashing and chlorhexidine application increased mortality by 17–18%). No data was available in an African setting for the effect of chlorhexidine cord care on neonatal mortality. Additionally, all the previous studies were done in settings with neonatal mortality rate of 40 deaths per 1000 livebirths or higher and almost all births took place in the community.

Added value of this study

Two studies (done in Pemba and Zambia) were designed to bridge the knowledge gap. This study, done in Pemba and combined with the mortality results from Zambia, is the first to our knowledge to provide data on the effect of chlorhexidine cord care on neonatal mortality and cord infections in an east African setting. Previous research did not address the issues raised by the WHO review about the effects of chlorhexidine in settings with hospital-based deliveries of more than 40% and with neonatal mortality rate of less than 30 deaths per 1000 livebirths. The study is unique in providing data on both omphalitis and neonatal mortality and showing a disconnect between a reduction in omphalitis and reduction in neonatal mortality, similar to the results of the Bangladesh study.

Implications of all the available evidence

All the available data (three Asian and two African studies) need to be reviewed using common methods and a meaningful meta-analysis needs to be done to guide the policy for use of chlorhexidine cord care in Asia and Africa. The data from African settings provided by this study combined with the results from Zambia might alter the global policy consensus about chlorhexidine cord care.

effective in reducing infections in the neonatal period.[13] Chlorhexidine is not expensive and, with a strong safety record, is a potential intervention in low-resource settings.[14,15] Chlorhexidine is included in the WHO model list of essential medicines for children.[16]

All trial sites in the studies in south Asia[7,8,11] had neonatal mortality rates of more than 35 deaths per 1000 livebirths, and nearly all births took place at home. A WHO expert panel discussed the possible role of chlorhexidine for cord care in low-resource community settings and emphasised the need for more studies from south Asia, as well as the need for similar trials in Africa.[17] In this community-based randomised trial, we aimed to investigate the effect of umbilical cord cleansing with 4% chlorhexidine solution on the rates of neonatal mortality and omphalitis in a rural setting in Tanzania. A similar trial was started at the same time in Zambia, the results of which are also published in *The Lancet Global Health*.[18]

Methods

Study design

We did a community-based randomised controlled trial on Pemba Island in the Zanzibar archipelago off the coast of east Africa, where the neonatal mortality rate was 25 deaths per 1000 livebirths and infant mortality rate was 89 deaths per 1000 livebirths.[19] More than 99% of the population are Shirazi Muslims and reside in an estimated 70 000 households on the island. The literacy rate of the population is 52%, and the birth rate is 8500–9000 births per year, about 40% of which take place at home (actual data collected during the study).[19]

The island has four district hospitals and a cottage hospital that provide outpatient and inpatient health services. At the community level, many government health centres provide basic maternal and child health (MCH) services. Other community-based health-care providers include trained or untrained traditional birth attendants (TBAs) at the village level and several over-the-counter drug outlets and traditional healers.

The study protocol was reviewed and approved by the institutional review board of the Johns Hopkins Bloomberg School of Public Health, USA, and the Zanzibar Medical Research and Ethics Committee, Tanzania. A joint technical advisory group (TAG) and data safety monitoring board (DSMB) for the Zambia and Pemba trials were established prior to study implementation.

Participants

All newborn babies from 1 h to 48 h of age born in hospital or the community (home based) on Pemba Island between May 19, 2011, and Aug 31, 2014, were eligible for inclusion in the study. The mother or father of the newborn baby must have been a permanent resident of the island, and the parents (or a literate witness if the parents were illiterate) must have given written consent to participate in the trial. Newborn babies with any congenital malformations that prevented application of intervention and babies

who needed to be admitted to hospital were excluded from the study.

As part of the pre-trial preparation (formative research phase), all the TBAs on the island and MCH staff were contacted and trained in the study procedures. Two study supervisors were stationed at each of the maternity wards of all the four major hospitals in Pemba (in two shifts) to cover deliveries occurring from 0700 h to 2000 h. Additionally, staff nurses were hired on a temporary basis. After delivery, the study team (consisting of hospital staff and a study supervisor) screened each newborn baby for eligibility to participate in the study. If the baby was eligible and clinically stable, the study procedure and purpose was explained to the mother. This information was explained to the nearest kin and their consent to participate was sought if the mother was not stable or was deceased. Neonates were enrolled in the study after consent was obtained. For enrolment in the community, all TBAs were provided with a mobile phone. Whenever a delivery took place, a conference call between the TBA, study supervisor of that area, and MCH staff was arranged to schedule a visit to the household. The study supervisor and MCH staff would then screen the newborn baby for eligibility and obtain consent accordingly.

Randomisation and masking

This study had two phases. During phase 1, participants were randomly assigned (1:1:1) to one of three intervention groups: treatment group using chlorhexidine, a control group using a placebo solution, and a control group with dry cord care. During phase 2 (Feb 20, 2013, onwards), the placebo solution was not used and the participants previously in that group were randomly assigned (1:1) to receive either chlorhexidine or dry cord care. This was done to facilitate combination of the findings with those from the Zambia trial (see Statistical analysis section). Randomisation was done using a computer-generated random sequence. The data for chlorhexidine and dry cord care groups from both phases of the study are presented in this Article. Other results from phase 1 will be presented in future papers.

For phase 1, chlorhexidine and placebo bottles were marked with 50 intervention codes (25 chlorhexidine and 25 placebo) by an independent member of the DSMB, assisted by a team of temporary workers. Each enrolled newborn baby was randomly assigned (1:2) to either dry cord or wet cord care. For babies allocated to wet cord care, a second stage of random assignment allocated the baby to one of the 50 intervention codes. Based on the distribution of villages and health-care centres, the study area was divided into 25 working areas with a study supervisor assigned to each area. Each supervisor was provided with two sets of envelopes. The first set contained the randomisation code to allocate a baby to the dry or wet group, and the second set of envelopes contained the randomisation codes to allocate the baby to one of the 50 intervention (chlorhexidine or placebo) codes. At the hospital, random assignment to wet or dry cord care was done by day of enrolment so that all babies born on a particular day were allocated to either the wet cord care or dry cord care. The second set of envelopes were opened on the wet cord day only to allocate the child to one of the 50 intervention codes. During phase 2, a new list was generated by the DSMB statistician to randomly assign babies (1:1) into dry and chlorhexidine cord care groups. Implementation was changed slightly, because the second envelope was not needed. Masking of allocation of intervention to workers and participants during phase 2 was not possible because of the nature of the interventions.

Procedures

The intervention used in the study was a solution of chlorhexidine gluconate (4% free chlorhexidine; Galantic Pharma, Mumbai, India). Stability, potency, colour, odour, and consistency of the solution were tested at three stages of the preparation and also tested twice at the field site. As per the findings of our initial study comparing different modes of administration of chlorhexidine solution for cord cleaning,[20] 10 mL opaque dropper bottles were used for administration.

All babies in the trial had an initial examination, and neonatal care messages were relayed to the mother or caretaker. For babies allocated to the chlorhexidine group and the placebo group (in phase 1), the MCH worker showed the mother or caretaker how to apply the solution to the baby, gave 3 days supply of the solution, and instructed the mother or caretaker to apply the solution to the cord every day including 3 days after the cord had dropped off. The mother or caretaker was informed that the MCH worker would visit again on day 4 and day 10 to apply the solution. On day 4, the worker delivered six more bottles to the household. The MCH staff provided a date chart and a pen for the mother to mark the days on which she applied the solution. The mothers were requested to keep the bottles after use and the empty bottles were collected on subsequent visits. For babies assigned to the dry cord care group, in addition to the initial examination, data collection, and neonatal care messages, TBAs and hospital staff instructed the mothers and caretakers not to cleanse the umbilical cord stump and to keep it dry.

Each family was visited on day 0 (day of enrolment), 1, 4, 10, and 28. At each visit, the study team (study supervisor and MCH staff) collected mortality and morbidity information on the baby from the mother or caretaker and examined the cord for redness, pus, swelling, and foul odour, and collected baseline data and demographic characteristics on the day of enrolment. Redness was categorised into four grades (none, mild, moderate, or severe). Mild redness was defined as restricted to the cord stump only; moderate as less than 2 cm extension onto the abdominal skin at

the base of the cord stump; and severe as spreading noticeably (>2 cm) outward from the base of the stump. If infection was suspected, the supervisor informed the district in charge, the district in charge then visited the household and examined the baby, took a photograph of the cord, and referred the mother to the nearest hospital if the cord was infected. MCH staff and the study supervisor revisited the household on day 28 to collect information regarding morbidity and hospital admission, and collected and reported the mortality information in cases of death. Cord infection signs recorded during multiple visits for all infants were combined and assessed for positive status according to the omphalitis definitions.

An electronic data capture system based on a netbook (small laptop) was used for collection of data. Each supervisor was provided with a netbook with the data collection software and pre-installed data uploading and backup plugin. Data from all netbook computers was backed up at the end of the day with universal serial bus (USB) drives, which were transported back to the central office (Public Health Laboratory Ivo de Carneri) the same evening and data downloaded to the central database server. The updated server database was uploaded to the same USB drive. The database in each netbook was replaced by the updated server database from the USB drive each morning before the start of work to ensure data consistency and integrity. We designed a robust data management system to help the teams plan their activities and quality control.

Outcomes

The primary outcome for this study was mortality until day 28. The secondary outcome was omphalitis occurring any time during first 10 days after birth. Any adverse events related to chlorhexidine use were noted.

Statistical analysis

During study design, the sample size was calculated on the assumption that the neonatal mortality rate in Pemba was 31 per 1000 livebirths and with a target of a 25% reduction in mortality. With 90% power and 5% two-sided type I error, and accounting for a 20% loss of deaths (due to death occurring before the intervention was started, loss to follow-up, or refusals), the sample size required was 11990 per group. The DSMB did two interim analyses in June, 2012, with a third of all enrolled newborn babies, and in June, 2014, with two-thirds of all enrolled babies. Because actual mortality rates were substantially lower than our original assumption, the DSMB recommended (in November, 2012) that the required sample size for the primary outcome of mortality with 80% power be 30000 per group. Based on the DSMB's recommendation and after approvals from institutional review boards, the placebo group of wet cord care was discontinued from Feb 20, 2013, onwards, to allow data from Pemba to be combined with that in Zambia,[18] which had chlorhexidine and dry cord care groups only. This decision was taken to provide a sample of reasonable power to assess the effect of chlorhexidine on neonatal mortality in sub-Saharan Africa. The study strategy did not change between phase 1 and phase 2.

To assess the effect of the intervention on mortality and omphalitis, intention-to-treat analyses included all enrolled babies. For babies whose families had moved out of the area or withdrawn from the study, data up until the date of censorship were included. We analysed survival of newborn babies in the first 28 days with Poisson regression models with the chlorhexidine group as the independent variable, using Stata (version 13). We used Cox survival regression models to reconfirm these results. Mortality was expressed as deaths per 1000 enrolled livebirths. Mortality outcomes were estimated overall, and stratified by place of birth (community or hospital), sex, first contact within 12 h, and birthweight. For births in hospital, day of enrolment was considered as a cluster; Poisson regression, with day of enrolment as the cluster variable, was done to adjust for the clustering effect. We assessed the estimated difference in treatment effect between hospital and community births by Mantel-Cox comparison between subgroups, estimating χ^2 for unequal relative rates (effect modification) and its p value (STMC procedure in Stata). Additionally, we built a regression model with death as the dependent variable and intervention group, place of birth, and interaction term (intervention × place of birth) as independent variables.

Risk estimates from both Pemba and Zambia were combined using the metan command in Stata. Primary data from both the studies were pooled and analysed using a Poisson regression model adjusting for the clustering effect (cluster-id as cluster variable in Zambia; day of enrolment for hospital births and study-id for community births in Pemba).

The trial is registered with ClinicalTrials.gov, number NCT01528852.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 19, 2011, and Aug 31, 2014, 47545 births were identified in the study area, from which 44232 newborn babies were enrolled into the study (figure). 36911 newborn babies were assigned to the chlorhexidine and dry cord care groups in phases 1 and 2. Of the 22097 babies enrolled during phase 1, 7484 (34%) were assigned to the dry cord care group and 7292 (33%) were assigned to the chlorhexidine group, with the remainder assigned to the placebo group, which was not

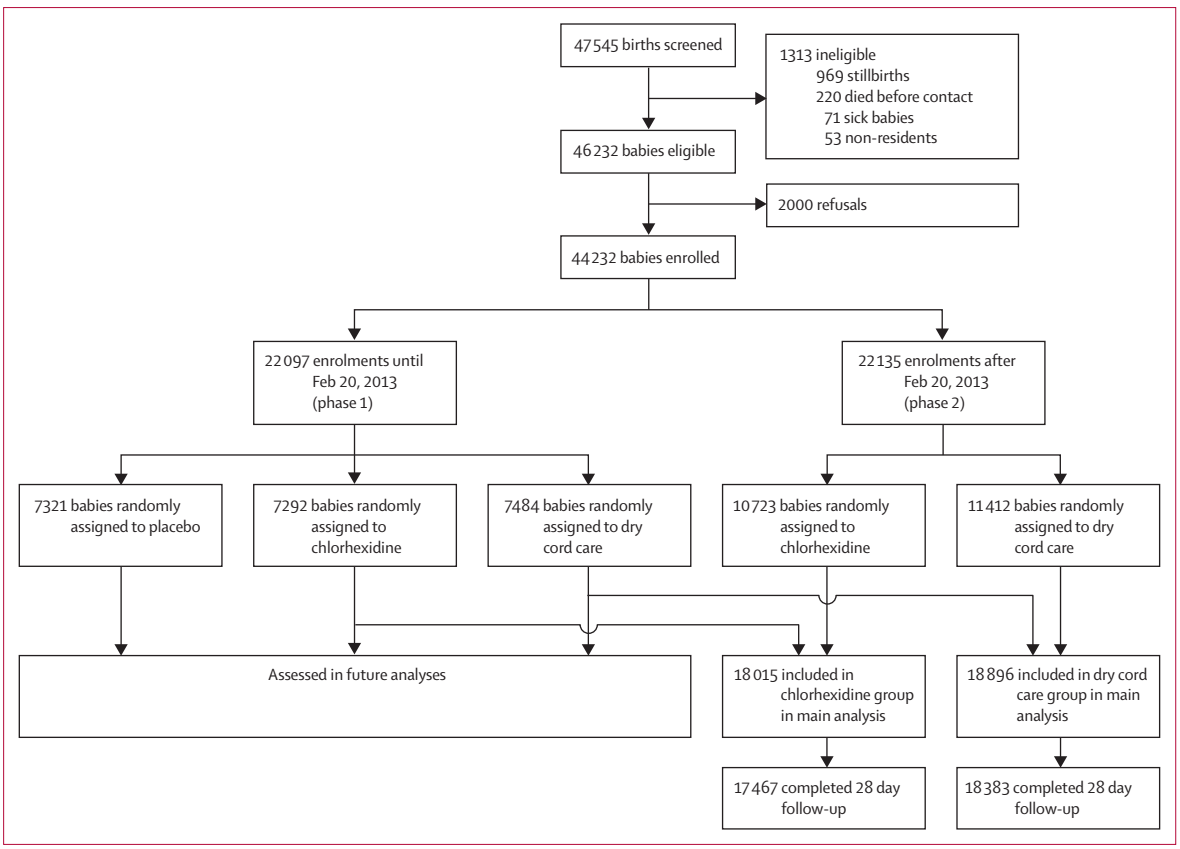

Figure: **Trial profile**

analysed further in this main outcomes study. Of the 22 135 babies enrolled during phase 2, 11 412 (52%) were in the dry cord care group and 10 723 (48%) were in the chlorhexidine group. There were no baseline differences in neonatal or parental demographic characteristics between the two groups (table 1). 19 426 (52·6%) of all 36 911 births took place in a hospital (table 1). 16 896 (93·8%) of 18 015 babies in the chlorhexidine group and 17 577 (93·0%) of 18 896 in the dry cord care group were contacted within 24 h of birth (table 2); 17 468 (97·0%) of 18 015 neonates in the chlorhexidine group were available for complete follow-up (28 days) compared with 18 384 (97·3%) of 18 896 neonates in the dry cord care group. 36 162 (98·0%) of babies attended all the planned visits (table 2).

Overall, neonatal deaths were reported in 221 (1·2%) babies in the dry cord care group compared with 189 (1·0%) babies in the chlorhexidine group. The risk of mortality after enrolment was not significantly different between the two groups (table 3). The risk of mortality did not differ by place of birth (relative risk [RR] 0·90, 95% CI 0·74–1·10; p=0·32; both treatment groups combined). Additionally, the model using intervention group, place of birth, and an interaction term between intervention and place of birth as independent variables calculated an RR of 0·97 (95% CI 0·65–1·45) for the interaction term and RR of 0·92 (0·67–1·27) for the intervention group. The sex of the baby and time of first application did not have a differential effect on mortality. There were no significant differences in the effect of chlorhexidine on early (first 7 days) or late (8–27 days) neonatal mortality (early mortality occurred in 140 [0·8%] of 18 015 babies in the chlorhexidine group *vs* 172 [0·9%] of 18 896 babies in the dry cord care group; late mortality occurred in 49 [0·3%] of 18 015 *vs* 49 [0·3%] of 18 896 babies).

Combination of the results from Pemba and Zambia (meta-analysis using random effects model) gave an RR of 0·99 (95% CI 0·80–1·23) for overall mortality risk by day 28 between chlorhexidine and dry cord care, whereas the combination of individual patient data (pooled analysis) gave an RR of 1·02 (0·86–1·20).

Babies in the chlorhexidine group had a lower risk of omphalitis with severe redness and pus (94% lower, 95% CI 74–98%) and of any redness or pus (35% lower, 30–39%) than did those in the dry cord care group (table 4).

Discussion

Within the constraints of reduced power caused by lower rates of mortality than expected in both treatment groups, we did not observe a significant reduction in neonatal mortality in the chlorhexidine group compared with the

	Chlorhexidine (n=18 015)	Dry cord care (n=18 896)
Parental occupation		
Father: fishing or farming	6440 (35·7%)	6728 (35·7%)
Mother: housewife	12 422 (69·0%)	13 019 (68·9%)
Parental literacy		
Paternal illiteracy	3472 (19·3%)	3487 (18·5%)
Maternal illiteracy	4916 (27·3%)	5012 (26·5%)
Household ownership	15 692 (87·1%)	16 383 (86·7%)
Maternal parity		
First or second child	3963 (22·0%)	4365 (23·1%)
Third or fourth child	5260 (29·2%)	5537 (29·3%)
Fifth or higher	8791 (48·8%)	8994 (47·6%)
Single or multiple birth		
Single	17 384 (96·5%)	18 178 (96·2%)
Twins	631 (3·5%)	718 (3·8%)
Sex of neonate		
Male	9201 (51·1%)	9589 (50·7%)
Female	8814 (48·9%)	9307 (49·3%)
Birthplace of neonate		
Hospital	9272 (51·5%)	10 154 (53·7%)
Community	8742 (48·5%)	8743 (46·3%)

Data are n (%).

***Table 1*: Baseline demographic neonatal, maternal, and household characteristics**

	Chlorhexidine (n=18 015)	Dry cord care (n=18 896)
Day 0 visit	18 015 (100%)	18 896 (100%)
Day 1 visit	17 820 (98·9%)	18 742 (99·2%)
Day 4 visit	17 702 (98·3%)	18 611 (98·5%)
Day 10 visit	17 620 (97·8%)	18 542 (98·1%)
All planned visits made	17 620 (97·8%)	18 542 (98·1%)
Excluding deaths	17 580 (98·6%)	18 504 (99·1%)
Timing of cord intervention		
Within 12 h	9721 (54·0%)	10 008 (53·4%)
13–24 h	7175 (39·8%)	7569 (40·1%)
>24 h	1119 (6·2%)	1239 (6·5%)

Data are n (%).

***Table 2*: Coverage and timing of intervention or visit**

dry cord care group, or when we combined these results from Pemba, Tanzania, with those from Zambia. Additionally, the 10% lower mortality rate reported in the chlorhexidine group was much smaller than that hypothesised based on the findings of the Asian trials.[11]

However, our findings did show that application of chlorhexidine significantly reduced the prevalence of omphalitis when compared with dry cord care. The risk of omphalitis was reduced by 24–39% for most grades of infection and was reduced by 94% for omphalitis when defined as severe redness with pus. These findings are consistent with those from earlier trials in Nepal,[7] Pakistan,[8] and Bangladesh.[11] Similar to our findings, the risk of cord infection in Nepal was reduced by 32–75% for different grades of infection in the chlorhexidine cleansing group, and in Bangladesh, newborn babies who had 7 days of chlorhexidine application were at a lower risk of any redness in the umbilical stump or pus than babies who had 1 day of chlorhexidine application. Results from the trial in Pakistan also showed a lower risk of omphalitis of any grade in babies in the chlorhexidine group than babies in the dry cord care group.

The umbilical cord stump of a newborn baby is a prime site of bacterial colonisation. Infection of the stump—omphalitis—poses a serious threat to the newborn baby and has been suggested to play an important role in systemic infection and mortality risk. The patency of the umbilical blood vessels in the first few days of life is known to provide access for pathogens to enter the blood stream even in the absence of omphalitis.[6,21,22] Hence, one possible explanation for the disparity in the effects of chlorhexidine between omphalitis and mortality could be the occurrence of sepsis without omphalitis. Sepsis in the absence of omphalitis can occur when the host immunity does not limit the infection to the umbilical stump, causing direct systemic infection without eliciting localised signs of omphalitis. Application of chlorhexidine on the cord stump might reduce the risk of local cord infection, but not prevent the pathogens from entering into the bloodstream through patent umbilical vessels, leading to sepsis and death.[23] Application of chlorhexidine is known to substantially delay cord separation. If the delay in cord separation perpetuates the risk of exposing the vessels to bacterial contamination,[24] it might have been responsible for the differences between 1 day versus 7 days of chlorhexidine application in the Bangladesh study and the inconsistency between omphalitis and mortality results in our study. Any risk related to delayed cord separation needs further investigation.

Before the start of the study, the neonatal mortality rate in sub-Saharan Africa was reported to be higher (31 deaths per 1000 livebirths) than in Pakistan (29 per 1000 livebirths),[8] Bangladesh (24 per 1000 livebirths), and Nepal (23 per 1000 livebirths).[4] However, mortality rates in Africa have changed substantially in the past decade. The observed per-protocol mortality rates in the chlorhexidine and dry cord care groups in our study (10·5 and 11·7 per 1000 livebirths, respectively), were much lower than we estimated. These rates were also lower than reported in studies in Bangladesh (22·5 and 28·3 deaths per 1000 livebirths, respectively) and Nepal (14·6 and 19·3 per 1000 livebirths, respectively). The low overall mortality rates in our study could be attributed to a general time trend as indicated by decline of neonatal mortality rate from 31 to 25 per 1000 livebirths in 2010[19] and 19 per 1000 livebirths in 2015.[1] The mortality rates recorded in this study could also have been affected by increased sensitisation of the mothers and other family members of cord care hygiene during the formative phase of the study,

and the prevalent cord care practices in this region. A study[25] done during the formative phase of this trial revealed that dry cord care is a well understood and practised concept in Pemba. Therefore, dry cord care might already have been better practised in this setting than in the Asian study populations. However, the effects on omphalitis would suggest that there was still a substantial risk of contamination of the cord stump in Pemba and any practice related to cord care would be unlikely to affect neonatal mortality. Even though the results from three trials of chlorhexidine for cord care show reduction of neonatal infections and deaths, these studies have not established the ideal timing and duration of chlorhexidine application.[26] With the conflicting results of 1 day and 7 day application of chlorhexidine in the trial in Bangladesh, further investigation is needed to understand the effects in Asia and sub-Saharan Africa.

By contrast with the previous trials in south Asia,[26] which predominantly enrolled home births (>90%) and were cluster randomised trials with potential for baseline differences, the strengths of our study are that this trial is an individually randomised controlled trial with a large sample size; we enrolled children both from community births (47%) and hospital births (53%); the proportion of babies contacted within 24 h was higher in our study, with 93% of first contacts made within 24 h in both groups, than in Bangladesh (86–88%) and in Nepal (62–64%), which should have improved the impact of chlorhexidine in our trial; and more than 95% of the screened and eligible newborn babies were included in the final analysis, thereby reducing selection bias.

A weakness of our study is that the independent power of the study is low because the observed mortality rates were lower than expected. However, along with a concomitant trial in Zambia,[18] we present important first evidence that chlorhexidine application on the umbilical cord has no effect on mortality in low-resource settings in sub-Saharan Africa. The study results and combined analysis suggest that chlorhexidine does not have a substantial impact on mortality in both settings.

The study area is comparable to other African countries in terms of limited resources, low rates of skilled attendance at birth, and unhygienic cord care practices.[7,8,11,18] In this study, we did not observe any differences in the effect of chlorhexidine on omphalitis or mortality between hospital births and community births. This argues against a lack of impact compared with Asian studies being due to higher hospital births in our setting.

The findings in our study suggest that use of chlorhexidine for the reduction of omphalitis is justified, but in an African setting there is insufficient evidence to promote this intervention to reduce neonatal mortality. In most African settings, mortality estimates are much lower than those reported by Demographic and Health Surveys, especially where prospective data have been collected. The low neonatal mortality rate observed in this trial (17 per 1000 livebirths [including deaths before randomisation] compared with 25 per 1000 livebirths reported by the Tanzania Demographic Health Survey[19]) is consistent with the situation in most African settings. A pooled analysis of the two African trials combined with the three Asia trials needs to be undertaken to inform policy. Such an analysis will require careful description of the different contexts (eg, community *vs* hospital delivery, low *vs* high neonatal mortality rate, and different cultural practices) and attention to weighting of the studies in the meta-analysis, quality scoring, and other related statistical details. This meta-analysis should be done under the coordination of WHO with the involvement of independent consultants in addition to the investigators.

	Chlorhexidine (n=18 015)		Dry cord care (n=18 896)		Relative risk (95% CI)	p value
	Deaths	Deaths per 1000 livebirths	Deaths	Deaths per 1000 livebirths		
Overall	189	10·5	221	11·7	0·90 (0·74–1·09)	0·27
Place of birth						
Hospital	116	12·5	142	14·0	0·89 0·70–1·14)	0·37
Community	73	8·4	79	9·0	0·92 (0·67–1·27)	0·63
Sex						
Male	107	11·6	123	12·8	0·91 (0·71–1·11)	0·46
Female	82	9·3	98	10·5	0·88 (0·66–1·18)	0·41
First contact						
≤12 h	111	11·4	123	12·2	0·90 (0·69–1·16)	0·42
≥12 h	78	9·4	97	11·0	0·84 (0·62–1·13)	0·24
Birthweight						
Low birthweight	29	66·7	32	67·1	0·99 (0·59–1·67)	0·98
Normal birthweight	56	8·1	54	7·2	1·14 (0·78–1·65)	0·50

***Table 3*: Neonatal mortality in the intention-to-treat population**

	Chlorhexidine (n=18 015)		Dry cord care (n=18 896)		Relative risk (95% CI)	p value
	N	n per 1000 livebirths	N	n per 1000 livebirths		
Any redness or pus	1413	78·4	2183	115·5	0·65 (0·61–0·70)	<0·0001
Any redness without pus	1051	58·4	1427	75·5	0·76 (0·70–0·82)	<0·0001
Moderate redness with pus or severe redness	166	9·2	286	15·1	0·61 (0·50–0·73)	<0·0001
Severe redness with pus	2	0·1	33	1·8	0·06 (0·02–0·26)	0·0001

***Table 4*: Omphalitis in the intention-to-treat population**

Contributors

All authors participated in the research and intervention design. SS, UD, and REB were involved in the conceptualisation of research, development of study protocol, analysis of data, and the preparation of manuscript. AD and UD were responsible for data management, field implementation, and preliminary analysis. SD was responsible for training and quality control for omphalitis, and contributed to manuscript writing and editing. SMAl and SMAm helped with the Pemba administrative system, community mobilisation, and provided leadership and supervision to team members. MHM provided administrative support. AY helped with the analysis and manuscript writing. All authors reviewed the paper and approved the final version.

Declaration of interests
We declare no competing interests.

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