Effectiveness of 4% chlorhexidine umbilical cord care on neonatal mortality in Southern Province, Zambia (ZamCAT): a cluster-randomised controlled trial

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Summary

Background Chlorhexidine umbilical cord washes reduce neonatal mortality in south Asian populations with high neonatal mortality rates and predominantly home-based deliveries. No data exist for sub-Saharan African populations with lower neonatal mortality rates or mostly facility-based deliveries. We compared the effect of chlorhexidine with dry cord care on neonatal mortality rates in Zambia.

Methods We undertook a cluster-randomised controlled trial in Southern Province, Zambia, with 90 health facility-based clusters. We enrolled women who were in their second or third trimester of pregnancy, aged at least 15 years, and who would remain in the catchment area for follow-up of 28 days post-partum. Newborn babies received clean dry cord care (control) or topical application of 10 mL of a 4% chlorhexidine solution once per day until 3 days after cord drop (intervention), according to cluster assignment. We used stratified, restricted randomisation to divide clusters into urban or two rural groups (located <40 km or ≥40 km to referral facility), and randomly assigned clusters (1:1) to use intervention (n=45) or control treatment (n=45). Sites, participants, and field monitors were aware of their study assignment. The primary outcomes were all-cause neonatal mortality within 28 days post-partum and all-cause neonatal mortality within 28 days post-partum among babies who survived the first 24 h of life. Analysis was by intention to treat. Neonatal mortality rate was compared with generalised estimating equations. This study is registered at ClinicalTrials.gov (NCT01241318).

Findings From Feb 15, 2011, to Jan 30, 2013, we screened 42 356 pregnant women and enrolled 39 679 women (mean 436·2 per cluster [SD 65·3]), who had 37 856 livebirths and 723 stillbirths; 63·8% of deliveries were facility-based. Of livebirths, 18 450 (99·7%) newborn babies in the chlorhexidine group and 19 308 (99·8%) newborn babies in the dry cord care group were followed up to day 28 or death. 16 660 (90·0%) infants in the chlorhexidine group had chlorhexidine applied within 24 h of birth. We found no significant difference in neonatal mortality rate between the chlorhexidine group (15·2 deaths per 1000 livebirths) and the dry cord care group (13·6 deaths per 1000 livebirths; risk ratio [RR] 1·12, 95% CI 0·88–1·44). Eliminating day 0 deaths yielded similar findings (RR 1·12, 95% CI 0·86–1·47).

Interpretation Despite substantial reductions previously reported in south Asia, chlorhexidine cord applications did not significantly reduce neonatal mortality rates in Zambia. Chlorhexidine cord applications do not seem to provide clear benefits for newborn babies in settings with predominantly facility-based deliveries and lower (<30 deaths per 1000 livebirths) neonatal mortality rates.

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Introduction

Substantial progress has been made towards accomplishment of the 4th Millennium Development Goal (MDG) to reduce worldwide under-5 child mortality, but many countries did not reach the target of a 75% reduction between 1990 and 2015.[1] Most of the reduction in under-5 mortality is due to interventions that affect the post-neonatal period; globally, 2·9 million newborn babies die each year.[2] Neonatal sepsis and prematurity have emerged as principal challenges to further reductions in neonatal mortality.[3]

Chlorhexidine cord washes have been evaluated as a strategy to reduce umbilical cord infections, sepsis, and neonatal mortality.[4] Although three previous studies[5–7] found that topical chlorhexidine umbilical cord washes reduced neonatal mortality, the efficacy of chlorhexidine has not been assessed in an African population, where neonatal mortality rates are lower, HIV prevalence is higher, and delivery setting and cultural practices regarding cord care substantially differ from those in south Asia.[8]

Dry cord care has been the long-standing recommendation of umbilical stump care for most newborn babies.[9] Updated WHO guidelines[10] recommend application of chlorhexidine to the umbilical stump

Research in context

Evidence before this study

We searched PubMed and the Cochrane Library databases with no date or language restrictions, using the following search terms: "chlorhexidine", "umbilical cord", and "omphalitis". We found 17 articles from our search. At the time of ZamCAT initiation (2011), only one trial (in Nepal) was published that showed reduced neonatal mortality rates (NMRs). Subsequently, two other community-based trials of chlorhexidine-cord cleansing were completed in Pakistan and Bangladesh. All three studies found decreased neonatal mortality associated with chlorhexidine cord applications and a meta-analysis reported a 23% reduction in NMR (relative risk [RR] 0·77, 95% CI 0·63–0·94). These three studies, comparing chlorhexidine to dry cord care, were undertaken in densely populated rural areas of south Asia with high NMRs (≥30 deaths per 1000 livebirths) and predominantly home deliveries. Limitations of the three studies include mixed findings in Bangladesh when examining one application, which significantly reduced NMR compared with once a day for 7 days application; factorial design in Pakistan where, when handwashing is removed, there was insufficient power to show that chlorhexidine significantly reduced NMR; and in Nepal, where only infants enrolled within 24 h of birth had a significant reduction in NMR.

Added value of this study

The rationale and design of ZamCAT and the Pemba Island studies advance the work of the previous trials in new settings in sub-Saharan Africa. The studies' sample sizes and design were guided by published reviews on the potential effect of chlorhexidine interventions on neonatal health outcomes and were developed in conjunction with each other. Provisional WHO guidelines released in September, 2012, when both studies were underway, recommended dry cord care with chlorhexidine application only in settings of high NMR (≥30 deaths per 1000 livebirths) and home delivery. The ZamCAT findings challenge the assumption that, if chlorhexidine works in south Asia, it must work in sub-Saharan Africa. In the Southern Province of Zambia, with a relatively high rate of facility-based deliveries (63%) and lower NMR (14·4 deaths per 1000 livebirths), chlorhexidine did not reduce neonatal mortality compared with dry cord care. When our results are pooled with those from the Pemba Island study, the combined analysis shows no evidence of a mortality benefit for chlorhexidine cord washes compared with dry cord care (NMR RR_{pooled} 1·02, 95% CI 0·86–1·20, and RR_{meta} 0·99, 95% CI 0·80–1·23).

Implications of all the available evidence

Current WHO chlorhexidine policy and guidelines might be appropriate in settings with high NMR and predominantly home deliveries. However, our results suggest that the global rollout of chlorhexidine is inappropriate, especially in low NMR settings in sub-Saharan Africa.

immediately after birth for home births and in environments with high neonatal mortality rates (>30 deaths per 1000 livebirths). Some donor and advocacy groups are proposing more extensive use of chlorhexidine and rapid programmatic scale-up globally, but generalisable evidence supporting the efficacy of this approach outside south Asia is scarce, with no evidence from Africa.[11] In view of the need to assess efficacy in an African population, we aimed to compare daily cord cleansing with 4% chlorhexidine with standard practice of dry cord care in Zambia's Southern Province. A similar trial was done in Pemba Island, Tanzania.[12]

Methods

Study design

We did a community-based, cluster-randomised controlled trial (the Zambia Chlorhexidine Application Trial [ZamCAT]) in Zambian Government or mission primary health-care centres in the Southern Province of Zambia (appendix). In 2007, this province had a neonatal mortality rate of 37 deaths per 1000 livebirths and maternal HIV prevalence of 14·5%.[13] The design and methods of ZamCAT have been reported elsewhere.[14] The unit of randomisation (clusters) was the study sites (Zambian Government or mission primary health-care centres and their catchment areas). Eligible health-care centres provided routine antenatal services and at least 160 annual births in their catchment area.

See Online for appendix

Participants

Study field monitors screened women attending antenatal care visits at eligible health centres and during community outreach activities for study enrolment. Eligible women were in their second or third trimester, aged 15 years or older, planning to stay in the catchment area until 28 days post-partum, and willing to provide informed consent and complete cord care as per cluster assignment. At enrolment, data were collected from women about previous and current pregnancies, previous obstetric complications, expected date of delivery, and their demographics. Participants were encouraged to deliver at their nearest health facility and were given standard newborn care messages—which included information about delivery location, breastfeeding, cord care, and danger signs of ill health in their newborn baby—as per national guidelines.[15,16]

At enrolment, study participants provided local contact information and study personnel with assistance from the study participant drew maps from the clinic to their home to allow field monitors to know where to go for the home visits. Before study initiation, investigators worked with local tribal and political leadership to develop

community-specific systems to notify field monitors about ZamCAT participant births within 24 h.[14] Contact methods included via a personal or facility-based mobile phone or sending of relatives or health providers to notify study personnel.

The Boston University Medical Campus Institutional Review Board and University of Zambia Research Ethics Committee provided ethical approval, and the Zambian Ministry of Health approved the study to be undertaken in Zambia. All women provided written informed consent, which was obtained in languages of English or Tonga.

Randomisation and masking

We used stratified, restricted randomisation[17] to divide clusters into three groups: urban, rural but located within 40 km of the nearest referral facility, and rural and located 40 km or more from the referral facility. In each group, clusters were randomly assigned (1:1) to either chlorhexidine treatment (intervention) or dry cord care (standard practice), with restriction to achieve balance among five factors: health-centre catchment population, total births, distance to referral facility, total facility staff, and number of associated community-based traditional birth attendants. Sites and participants were aware of their study assignment, as were field monitors.

Procedures

Field monitors made five home visits—one antenatal and four postnatal (day 1, 4, 10, and 28 post-partum). The antenatal visit was completed within 2 weeks of enrolment, during which the field monitor confirmed the home location for follow-up, provided a standard clean delivery kit (which included soap, sterile razor blade, sterile gloves, two cord clamps, candle and matches, and a plastic mat) to all study participants irrespective of study group, reviewed study procedures with the mother, and screened for pregnancy danger signs.

In the chlorhexidine group, field monitors provided pregnant women with chlorhexidine and cotton swabs at the antenatal home visit, and instructed them on how to apply chlorhexidine to the umbilical stump. Liquid 4% chlorhexidine formulation was supplied in single-application 10 mL eyedropper bottles (Galentic Inc, Mumbai, India). Each mother in the chlorhexidine group received instructions and sufficient quantities for once a day application until 3 days after the umbilical stump had separated fully. The birth attendant, mother, or a relative applied the first dose; the mother or her family completed subsequent applications. Participants in the dry cord care group were instructed by field monitors to keep the cord clean, dry, and free of topical substances, in accordance with the Zambian Ministry of Health policy.[15]

At the postnatal visits, field monitors assessed and documented the mother's and newborn baby's health status and adherence to cluster-specific cord care. Mothers were asked whether any substances had been applied to the cord, including chlorhexidine and

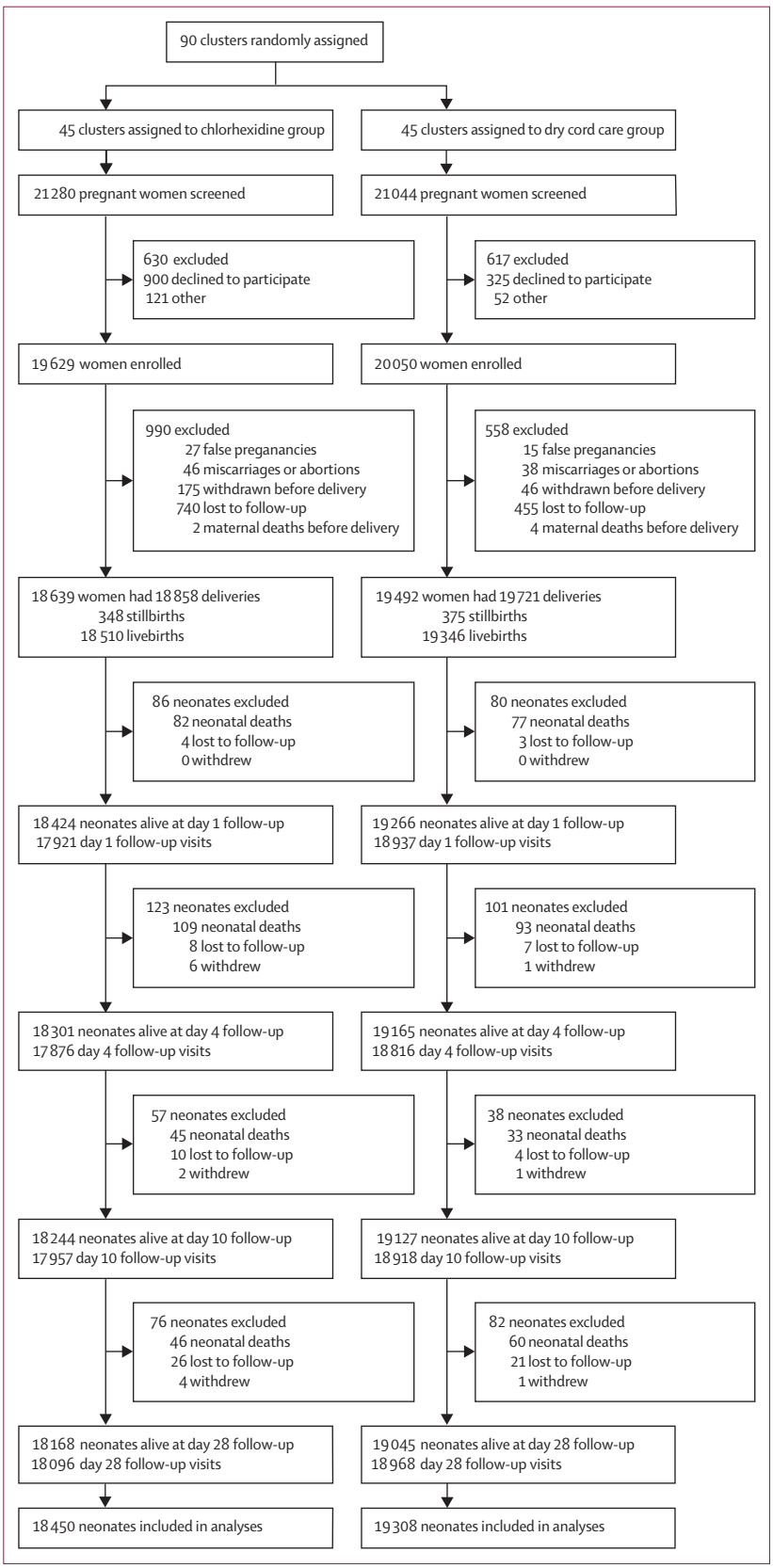

Figure 1: **Trial profile**

	Chlorhexidine (n=19 629)	Dry cord care (n=20 050)
Age	(n=19 455)	(n=19 896)
<20 years	4671 (24·0%)	4580 (23·0%)
20–35 years	12 772 (65·6%)	13 122 (66·0%)
>35 years	2012 (10·3%)	2194 (11·0%)
Median household size (IQR)	6 (4–8)	6 (4–8)
Woman's highest level of education	(n=19 460)	(n=19 904)
No education	1936 (9·9%)	1958 (9·8%)
Lower primary (grade 1–4)	2293 (11·8%)	2563 (12·9%)
Upper primary (grade 5–7)	7731 (39·7%)	7874 (39·6%)
Junior secondary (grade 8–9)	5422 (27·9%)	5499 (27·6%)
Upper secondary (grade 10–12)	1895 (9·7%)	1840 (9·2%)
>Upper secondary	180 (0·9%)	160 (0·8%)
Do not know	3 (0·02%)	10 (0·1%)
Ethnic origin or tribe	(n=19 461)	(n=19 912)
Tonga	17 003 (87·4%)	17 650 (88·6%)
Ila	105 (0·5%)	121 (0·6%)
Lozi	786 (4·0%)	795 (4·0%)
Nyanja	525 (2·7%)	432 (2·2%)
Bemba	413 (2·1%)	433 (2·2%)
Other	629 (3·2%)	481 (2·4%)
Marital status	(n=19 463)	(n=19 910)
Single	3021 (15·5%)	3133 (15·7%)
Married	16 107 (82·8%)	16 499 (82·9%)
Separated, divorced, or widowed	224 (1·2%)	187 (0·9%)
Cohabiting	109 (0·6%)	89 (0·4%)
Missing	2 (0·01%)	2 (0·01%)
Maternal literacy ability	(n=19 441)	(n=19 903)
Not at all	5037 (25·9%)	5491 (27·6%)
A bit	8835 (45·4%)	9516 (47·8%)
Very well	5492 (28·2%)	4835 (24·3%)
No response	77 (0·4%)	61 (0·3%)
Household water source	(n=19 439)	(n=19 875)
Household tap	1861 (9·6%)	1715 (8·6%)
Community tap	1919 (9·9%)	1761 (8·9%)
Other water source on own property	2295 (11·8%)	2403 (12·1%)
Community well or river	13 241 (68·1%)	13 768 (69·3%)
No answer	56 (0·3%)	62 (0·3%)
Other	67 (0·3%)	166 (0·8%)
Housing roof type	(n=19 394)	(n=19 853)
Iron sheets or asbestos	8854 (45·7%)	8241 (41·5%)
Thatched grass	10 462 (53·9%)	11 531 (58·1%)
Do not know	36 (0·2%)	37 (0·2%)
Other	42 (0·2%)	44 (0·2%)
Housing wall materials	(n=19 446)	(n=19 904)
Cement bricks without plaster	763 (3·9%)	767 (3·9%)
Cement bricks with plaster	2017 (10·4%)	1971 (9·9%)
Other bricks without plaster	12 780 (65·7%)	13 021 (65·4%)
Other bricks with plaster	2608 (13·4%)	2998 (15·1%)
Mud and poles	1196 (6·2%)	1063 (5·3%)

(Table 1 continues in next column)

	Chlorhexidine (n=19 629)	Dry cord care (n=20 050)
(Continued from previous column)		
Do not know	1 (0·005%)	3 (0·02%)
Other	81 (0·4%)	81 (0·4%)
Ownership of a TV or radio	(n=19 408)	(n=19 870)
No	6909 (35·6%)	7433 (37·4%)
Radio	8390 (43·2%)	8614 (43·4%)
Television	613 (3·2%)	511 (2·6%)
Both	3496 (18·0%)	3312 (16·7%)
Household light source	(n=19 448)	(n=19 891)
Electricity	1661 (8·5%)	1378 (6·9%)
Lantern (kerosene lamp)	1923 (9·9%)	2219 (11·2%)
Candle	3335 (17·1%)	3308 (16·6%)
Battery	11 506 (59·2%)	10 943 (55·0%)
Other	1023 (5·3%)	2043 (10·3%)
Time walking from home to health facility	(n=19 412)	(n=19 854)
<1 h	6404 (33·0%)	6784 (34·2%)
1 h to <2 h	6854 (35·3%)	7239 (36·5%)
2 h to <3 h	4179 (21·5%)	4207 (21·2%)
3 h to <4 h	1425 (7·3%)	1093 (5·5%)
4 h to <5 h	284 (1·5%)	329 (1·7%)
≥5 h	212 (1·1%)	81 (0·4%)
Unknown	54 (0·3%)	121 (0·6%)
Parity	2·4 (2·3)	2·5 (2·4)
Gravida	3·5 (2·3)	3·6 (2·4)
Had a previous child die in neonatal period	1536/18 366 (8·4%)	1707/19 188 (8·9%)
Gestational age at enrolment based on LMP (weeks)	28·0 (7·2)	28·4 (7·2)
Bed net previous night*	11 092/19 402 (57·2%)	11 783/19 858 (59·3%)

Data are n (%), n/N (%), or mean (SD). LMP=last menstrual period. *Slept under a mosquito bed night before study enrolment.

Table 1: **Demographic, household, and pregnancy characteristics of women enrolled**

non-study applications. Field monitors directly examined the umbilical cord until detachment and thereafter the umbilical stump, and collected empty chlorhexidine bottles as confirmation of use. These assessments were done at each of the four visits. Any mother or newborn baby with danger signs or symptoms was referred to the health-care centre. HIV status was recorded from the woman's antenatal clinic card; infants exposed to HIV were referred to the health centre if they had not received antiretroviral prophylaxis at delivery.

Field monitors collected data using forms designed in the TeleForms system (HP, Cambridge, UK). Supervisors reviewed forms for completeness and the forms were then scanned, entered, and exported into a Microsoft Access database (accessed by KEAS and AZ, who knew of participant group assignments). If forms were incomplete, field supervisors requested field monitors

gather the data needed, but if they could not the data were deemed missing. A data safety monitoring board completed two interim analyses at one-third and two-thirds accrual.[17]

Outcomes

The primary outcomes were all-cause neonatal mortality within 28 days post-partum and all-cause neonatal mortality within 28 days post-partum among babies who survived the first 24 h of life. Deaths were documented by interview with the mother; stillbirths were defined as an infant who did not breathe, cry, or move at the time of delivery. Information was recorded on the time of birth and death, and surrounding circumstances. Secondary outcomes, reported here, were incidence of omphalitis (any level of severity; as defined by umbilical stump erythema or purulent discharge), on the basis of field monitors' assessment at each study visit. Additional secondary outcomes included proportion of women who deliver at a site other than their intended delivery location and factors affecting where pregnant women deliver (which will be reported elsewhere), and characterisation of health service network available to pregnant and post-partum women and their children, which has been reported elsewhere.[18] Adverse events were defined as chlorhexidine-related events including accidental ingestion, accidental ocular exposure, contact dermatitis, or skin irritation around the umbilical stump, and anaphylaxis. A technical advisory group convened twice during the study to review study progress.

Statistical analysis

Even though a mortality reduction of 34% was reported in Nepal,[5] we used a more conservative 25% reduction for the sample size calculations. Assuming that the national neonatal mortality rate of 37 deaths per 1000 births included stillbirths or early neonatal deaths (Zambia Demographic Health Survey [DHS] 2007), we expected the dry cord care neonatal mortality rate to be 29 deaths per 1000 livebirths. With 90% power to detect a 25% reduction of the neonatal mortality rate from 29 deaths per 1000 livebirths in the dry cord care group (k=0·20 and α=0·05), 90 clusters with 320 births per cluster were needed (total sample size 28 800 newborn babies or 14 400 babies per group). To account for any potential loss to follow-up, we increased the sample size by 10%. Just before initiation of recruitment, a meta-analysis[19] of chlorhexidine studies reported a 17% mortality reduction. The technical advisory group therefore recommended a revised sample size of 42 570 newborn babies (473 women per cluster) to detect a similar all-cause neonatal mortality rate reduction. We used an intention-to-treat (ITT) analysis for both primary and secondary outcomes. In response to reviewer requests, we also did a post-hoc pooled analysis of our primary outcomes together with those of the similar trial done in Pemba Island, Tanzania.[12] Risk estimates from both Pemba Island and Zambia were combined using metan command in Stata. Primary data from both studies were pooled and analysed with Poisson regression model, adjusting for clustering.

We examined the effect on neonatal mortality of the timing of first chlorhexidine wash (<24 h or ≥24 h after birth) compared with dry cord care. In the per-protocol population, we used propensity-scores analysis to compare those who applied chlorhexidine in the first 24 h of life to a matched subset of those in the dry cord care group. Characteristics matched included presence of danger signs in the child, maternal age, maternal education, and delivery location. We calculated risk ratios (RR; 95% CIs) using generalised estimating equations (GEE) models, using an exchangeable correlation matrix,

	Chlorhexidine (n=18 510)	Dry cord care (n=19 346)
Antenatal visits attended	3·3 (0·0)	3·4 (0·0)
Male infant	9055/18 155 (49·9%)	9396/19 081 (49·2%)
Low birthweight (<2500 g)	849/11 337 (7·5%)	836/12 085 (6·9%)
Mean birthweight (g [SD])	3101·8 (495·8)	3117·5 (503·1)
Premature (<37 weeks; based on last menstrual period)	3484/16 763 (20·8%)	3521/17 286 (20·4%)
HIV-exposed neonate	(n=17 878)	(n=18 877)
Reactive	1612 (9·0%)	1461 (7·7%)
Non-reactive	15 999 (89·5%)	17 273 (91·5%)
Unavailable	267 (1·5%)	143 (0·8%)
Place of delivery	(n=18 155)	(n=19 014)
Hospital	2068 (11·4%)	3057 (16·1%)
Health-care centre	9388 (51·7%)	9147 (48·1%)
Home	6509 (35·9%)	6682 (35·1%)
Other	190 (1·0%)	128 (0·7%)
Delivery attendant	(n=17 822)	(n=18 626)
Nurse or midwife	10 182 (57·1%)	10 260 (55·1%)
Trained traditional birth attendant	2174 (12·2%)	2556 (13·7%)
Untrained traditional birth attendant	692 (3·9%)	446 (2·4%)
Family member or relative	4030 (22·6%)	4400 (23·6%)
Mother delivered alone	487 (2·7%)	567 (3·0%)
Other	257 (1·4%)	397 (2·1%)
Used razor blade provided in CDK	15 453/18 008 (85·8%)	16 928/18 884 (89·6%)
Used gloves provided in CDK	17 558/18 008 (97·5%)	18 217/18 884 (96·5%)
Delivery mode	(n=17 831)	(n=18 750)
Vaginal	17 549 (98·4%)	18 387 (98·1%)
Vaginal with forceps	61 (0·3%)	123 (0·7%)
Vaginal with vacuum	20 (0·1%)	13 (0·1%)
Caesarean section	201 (1·1%)	227 (1·2%)
Drying of infant	(n=17 542)	(n=18 366)
Before the placenta was delivered	13 055 (74·4%)	12 804 (69·7%)
After the placenta was delivered	3874 (22·1%)	4707 (25·6%)
Baby not dried before being wrapped	102 (0·6%)	233 (1·3%)
Do not know	511 (2·9%)	622 (3·4%)
Breastfeeding initiated in ≤1 h after delivery	15 825/17 729 (89·3%)	16 761/18 781 (89·2%)

Data are mean (SD), n (%), or n/N (%). CDK=clean delivery kit.

Table 2: **Characteristics of infants born alive in Southern Province, Zambia**

	Chlorhexidine (n=18 510)	Dry cord care (n=19 346)
Applied chlorhexidine until 3 days after cord dropped off	15 949 (92·0%)*	..
First application ≤24 h of birth	16 660 (90·0%)	..
First application ≤48 h of birth	17 815 (96·2%)	..
No chlorhexidine application	396 (2·1%)	..
One application of chlorhexidine	69 (0·4%)	..
Two or more applications of chlorhexidine	18 045 (97·5%)	..
Days of chlorhexidine application	9·3 (2·5)	..
Non-study cord application made	1699 (9·2%)	2450 (12·7%)
Participant follow-up		
Day 1	17 921 (96·8%)	18 937 (97·9%)
Day 4†	17 876 (97·7%)	18 816 (98·2%)
Day 10‡	17 957 (98·4%)	18 918 (98·9%)
Day 28§	18 096 (99·6%)	18 968 (99·6%)

Data are n (%), or mean (SD). *Of 17 332 infants. †Denominator is 18 301 infants in the chlorhexidine group and 19 165 in the dry cord care group. ‡Denominator is 18 244 infants in the chlorhexidine group and 19 127 in the dry cord care group. §Denominator is 18 168 infants in the chlorhexidine group and 19 045 in the dry cord care group.

Table 3: **Chlorhexidine compliance, umbilical cord applications, and study follow-up (n=37 856 livebirths)**

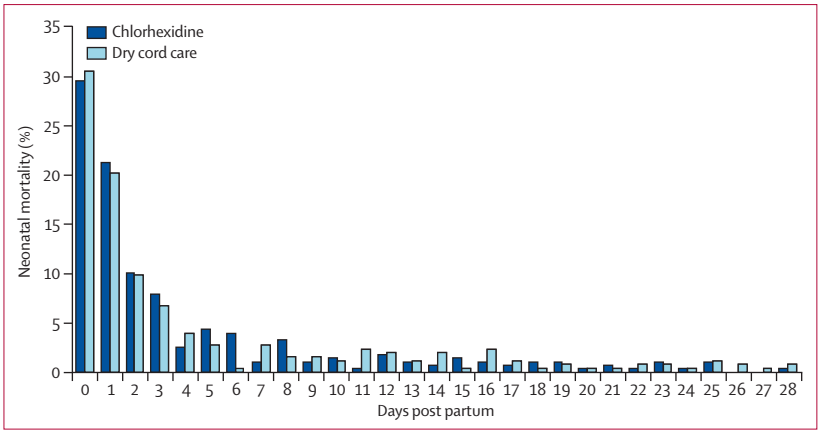

Figure 2: **Neonatal mortality by day of age at death, by study group**
545 deaths during 28 days post-partum.

accounting for clustering by health facility for all analyses (ITT and per protocol).

Baseline characteristics potentially associated with the outcomes were compared between the two groups using appropriate tests. Variables were compared between groups using the χ^2 test, Fisher's exact test, *t*-tests, or non-parametric Wilcoxon rank sum tests, as appropriate for continuous or categorical variables. We investigated the effects of adjusting for baseline characteristics. Key covariates considered for inclusion were sex, low birthweight (<2500 g), prematurity (gestational age <37 weeks based on last menstrual period), maternal age, maternal education, parity, birth location, distance from health facility, frequency of application of non-study substances to the umbilical cord, and exclusive breastfeeding. All statistical analyses were completed using SAS (version 9.3). This study is registered at ClinicalTrials.gov, number NCT01241318.

Role of the funding source

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

Results

From Feb 15, 2011, to Jan 30, 2013, we screened 42 536 pregnant women from 90 eligible clusters (12 urban, 56 rural ≤40 km from road, and 22 rural sites >40 km from road).[14] 41 110 (97·0%) women were eligible, of whom 39 679 (96·5%) were enrolled (figure 1). The mean enrolment per cluster was 436·2 women (SD 65·3) in the chlorhexidine group (45 clusters) and 445·5 women (59·5) in the dry cord care group (45 clusters). Before delivery, 1542 (3·8%) women were lost to follow-up, withdrew, had false pregnancies, or had spontaneous or elective abortions; six women died. 38 131 women delivered 38 579 children (443 sets of twins and five sets of triplets)—723 stillbirths and 37 856 livebirths. 37 690 (99·6%) newborn babies survived the first 24 h. Of all livebirths, 18 450 (99·7%) newborn babies in the chlorhexidine group and 19 308 (99·8%) newborn babies in the dry cord care group were followed up to day 28 post-partum or death.

Maternal sociodemographic and health characteristics, as well as labour and delivery practices, were similar between treatment groups (tables 1 and 2). Of all livebirths, 87·8% used the surgical blade from the clean delivery kit for cord cutting; 35·4% delivered at home, and 63·8% delivered in a health facility.

In the intervention group, 16 660 (90·0%) babies had chlorhexidine applied on the day of delivery and 18 114 (97·9%) babies had at least one chlorhexidine application (table 3). A slightly higher number of babies in the dry cord care group had non-chlorhexidine applications than in the intervention group (table 3).

Overall, the neonatal mortality rate at 28 days post-partum was lower than expected (14·4 deaths per 1000 livebirths); 30% of all 545 neonatal deaths occurred on the day of birth (day 0; figure 2). The all-cause neonatal mortality rate was not significantly different between groups (15·2 deaths per 1000 livebirths in the chlorhexidine group *vs* 13·6 deaths per 1000 livebirths in the dry cord care group; RR 1·12, 95% CI 0·88–1·44; table 4). With the ITT analysis limited to newborn babies who survived the first 24 h, the neonatal mortality rate in the chlorhexidine group was slightly higher than in the

dry cord care group (RR 1·12, 95% CI 0·86–1·47). In the as practiced analysis by use of a propensity score approach, with intervention group limited to newborn babies who survived the first 24 h, the neonatal mortality rate was 8·5 deaths per 1000 livebirths for those with chlorhexidine applied on the day of delivery and was 9·3 deaths per 1000 livebirths in the dry cord care group (RR 0·94, 95% CI 0·72–1·22).

Chlorhexidine application was not associated with decreased neonatal mortality in any of the pre-specified stratified analyses (table 5). Specifically no differences were noted in neonatal mortality rate for babies who were born premature or of low birthweight, whose mothers had known HIV status, or who were born in health-care facilities versus at home (table 5).

Omphalitis was diagnosed in 200 (0·5%) newborn babies, of whom 82 (41%; 4·43 cases per 1000 livebirths) were in the chlorhexidine group and 118 (59%; 6·10 cases per 1000 livebirths) were in the dry cord care group (RR 0·73, 95% CI 0·47–1·13). The finding did not differ substantially when restricted to babies with chlorhexidine applied in the first 24 h (0·76, 0·48–1·18; table 6).

Nine adverse events associated with chlorhexidine were reported; one case was of ocular exposure (grade 2 and did not require hospital admission) and eight episodes were of local skin irritation (grade 1). No cases of accidental ingestion, contact dermatitis, or anaphylaxis were reported.

	Livebirths	Neonatal deaths	NMR per 1000 livebirths	Relative risk (95% CI)*
Intention-to-treat analysis (primary outcomes)				
All-cause neonatal mortality (including day 0 deaths)				
All livebirths	37 856	545	14·4	
Chlorhexidine	18 510 (48·9%)	282 (51·7%)	15·2	1·12 (0·88–1·44)
Dry cord care	19 346 (51·1%)	263 (48·3%)	13·6	
All-cause neonatal mortality (excluding day 0 deaths)				
All livebirths who survived day 0	37 690	386	10·2	
Chlorhexidine	18 424 (48·9%)	200 (51·8%)	10·9	1·12 (0·86–1·47)
Dry cord care	19 266 (51·1%)	186 (48·2%)	9·7	
As practised analysis				
All-cause neonatal mortality (excluding day 0 deaths)				
All livebirths	35 871	327	9·11	..
Chlorhexidine†	16 645	141 (0·8%)	8·5	0·88 (0·66–1·16)
Dry cord care	19 266	186 (1·0%)	9·7	
Propensity-score analysis (excluding day 0 deaths)‡				
Chlorhexidine†	16 400 (50%)	132 (0·8%)	8·0	0·94 (0·72–1·22)
Dry cord care	16 400 (50%)	141 (0·9%)	8·6	

NMR=neonatal mortality rate. *Generalised estimating equations were used to adjust point estimate and CIs for cluster-randomised design. †Chlorhexidine applied ≤24 h after birth. ‡Denominator is 32 800 births.

***Table 4*: Neonatal mortality by study group**

Discussion

Chlorhexidine did not reduce neonatal mortality compared with dry cord care in the Southern Province of Zambia. Chlorhexidine was not more effective in either the ITT analysis or the as practised analyses in reducing neonatal mortality. Stratified analyses examining delivery location, birthweight, prematurity, and maternal HIV status also did not show significant reductions in neonatal mortality rate. With the need for simple interventions to prevent neonatal mortality in low-income and middle-income settings, chlorhexidine has appeared promising based on data in south Asia. However, in the context of relatively high rates of facility delivery (63%) and lower neonatal mortality rate (14·4 deaths per 1000 livebirths), chlorhexidine did not reduce neonatal mortality in Zambia.

In this large, cluster-randomised controlled trial with more than 37 800 liveborn children, less than 4% of enrolled women were lost before delivery, and less than 1% were lost to follow-up during the neonatal period. Compliance in the chlorhexidine and dry cord care groups was excellent, with low levels of non-study substances applied to the umbilical stump. The study was designed as an effectiveness trial, a real-world scenario in which the mother, attendant, or family member would apply the chlorhexidine rather than study personnel.

The study has several limitations. First, the observed neonatal mortality rate in the dry cord care group was 50% lower than the expected neonatal mortality rate (37 deaths per 1000 livebirths).[13] This low figure might be partly due to the package of services that all women in the study received—clean delivery kit, referral to clinic in the presence of maternal or neonatal danger signs, newborn health messages, in addition to antenatal clinic visits, and home visits in the early neonatal period. One aspect of this messaging, which was equally applied in the dry cord care and chlorhexidine groups, was an emphasis on keeping the cord clean and dry. The repeated cord care messages were done in an attempt to have the dry cord care group closely adhere to WHO guidelines. However, these similarities between groups might have resulted in better cord care practices in the context of the trial and thereby resulted in lower neonatal mortality rates in both groups. Additionally, the baseline neonatal mortality rate data were based on the 2007 Zambia DHS.[13] By contrast, the 2013–14 Zambia DHS revealed a neonatal mortality rate of 24 deaths per 1000 livebirths, so neonatal mortality has been progressively decreasing in Zambia during this period. Notably, the neonatal mortality rate had decreased from 37 deaths to 23 deaths per 1000 livebirths in Southern

	Livebirths	Neonatal deaths	NMR per 1000 livebirths	Relative risk* (95% CI)
Birthweight (n=23 422)				
Low birthweight (<2500 g)				
Chlorhexidine	849 (3·6%)	21 (0·1%)	24·7	0·73 (0·39–1·37)
Dry cord care	836 (3·6%)	28 (0·1%)	33·4	..
Normal birthweight (≥2500 g)				
Chlorhexidine	10 488 (44·8%)	57 (0·2%)	5·4	1·33 (0·87–2·05)
Dry cord care	11 249 (48·0%)	46 (0·2%)	4·1	..
Prematurity (n=34 039)				
Premature (<37 weeks)				
Chlorhexidine	3484 (10·2%)	111 (0·3%)	31·9	1·03 (0·74–1·44)
Dry cord care	3521 (10·3%)	109 (0·3%)	31·0	..
Normal gestational age (≥37 weeks)				
Chlorhexidine	13 269 (30·9%)	135 (0·4%)	10·2	1·16 (0·86–1·59)
Dry cord care	13 765 (40·4%)	120 (0·4%)	8·7	..
Maternal HIV status known (n=36 593)				
Infant exposed to HIV (n=3103)				
Chlorhexidine	1631 (52·6%)	38 (1·2%)	23·2	1·14 (0·62–2·11)
Dry cord care	1472 (47·4%)	30 (1·0%)	20·4	..
Infant not exposed to HIV (n=33 490)				
Chlorhexidine	15 999 (47·8%)	220 (0·7%)	13·7	1·13 (0·87–1·44)
Dry cord care	17 273 (51·6%)	211 (0·6%)	12·2	..
Delivery location (n=37 165)				
Health facility or hospital (n=23 658)				
Chlorhexidine	11 455 (48·4%)	177 (0·7%)	15·5	1·09 (0·82–1·46)
Dry cord care	12 203 (51·6%)	172 (0·7%)	14·1	..
Home delivery (n=13 507)				
Chlorhexidine	6698 (49·6%)	95 (0·7%)	14·2	1·25 (0·86–1·83)
Dry cord care	6809 (50·4%)	77 (0·6%)	11·3	..

Data are n (%), unless otherwise specified. NMR=neonatal mortality rate. *Generalised estimating equations were used to adjust point estimate and CIs for cluster-randomised design.

Table 5: **Neonatal mortality by pre-specified health indicators**

	Livebirths	Cases	Risk per 1000 livebirths	Relative risk* (95% CI)
Intention-to-treat analysis				
All livebirths	37 856	200	5·28	..
Chlorhexidine	18 510 (49·0%)	82 (41·0%)	4·43	0·73 (0·47–1·13)
Dry cord care	19 346 (51·2%)	118 (59·0%)	6·10	..
As practiced analysis				
Chlorhexidine†	16 660 (46·3%)	77 (39·5%)	4·62	0·76 (0·48–1·18)
Dry cord care	19 346 (53·7%)	118 (60·5%)	6·10	..

*Generalised estimating equations were used to adjusted point estimate and CIs for cluster-randomised design. †First application <24 h after birth.

Table 6: **Omphalitis incidence in newborn babies**

Province. Thus, secular trends existed, resulting in lower neonatal mortality rates than expected during the study period in addition to trial-specific interventions that might have further lowered all-cause neonatal mortality rates, and which resulted in the study being underpowered. However, a pooled analysis of our Zambian and the completed Pemba Island[12] data, with roughly double the sample size, showed no suggestion of a benefit of chlorhexidine on neonatal mortality (RR_{pooled} 1·02, 95% CI 0·86–1·20, and RR_{meta} 0·99, 95% CI 0·80–1·23).

Only 89% (37 856 of 42 570) of the target sample size was attained. When we completed a post-hoc power calculation (as previously described) with the obtained sample size and observed neonatal mortality rate, we had 80% power to detect a 28% reduction in neonatal mortality rate, which is greater than the reduction observed in the south Asian data meta-analysis, but more in line with observations in Nepal[20] and Pakistan.[6,19] The observed incidence of omphalitis was lower than expected; it is possible that mild or moderate cases were under-reported as diagnosis was based on purulent discharge or redness at the umbilical stump.

To date, the evidence base for a global chlorhexidine policy recommendation has been limited to three cluster-randomised community-based studies[5–7,19] in south Asia comparing chlorhexidine cord washes to dry cord care. A cluster-randomised trial in Nepal[5] reported a trend towards lower neonatal mortality among all neonates receiving daily chlorhexidine, lower mortality among neonates receiving chlorhexidine in the first 24 h after birth, and significantly less omphalitis than in neonates receiving dry cord care. A study[7] with three groups undertaken in rural Bangladesh showed a significant reduction in neonatal mortality in the group who received a single umbilical cord cleansing on day 1 post partum, but counterintuitively did not show a similar effect in neonates who had daily umbilical cord washes for 7 days post-partum.[7] Finally, in rural Pakistan,[6] daily chlorhexidine cord applications resulted in significant reductions in neonatal mortality and omphalitis.[6] All three studies[5–7] comparing chlorhexidine with dry cord care were completed in densely-populated rural areas of south Asia with high neonatal mortality rates (≥30 deaths per 1000 livebirths) and predominantly home deliveries.

The reported effect of chlorhexidine on neonatal mortality observed in Nepal, Bangladesh, and Pakistan from 2002 to 2009 might not be generalisable to many sub-Saharan African countries where antenatal care services are used more frequently, there are more facility-based deliveries, and, in some settings, a lower neonatal mortality rate.[21] Global efforts to encourage facility-based deliveries to reduce maternal mortality might be blunting the benefits of chlorhexidine for neonates. Additionally, overall secular trends towards lower neonatal mortality globally might contribute towards the non-effect of chlorhexidine.[21–23] Important differences exist between the

south Asian and Zambian populations regarding cord care, newborn health, and other newborn-care practices. In our Zambian study, 63% of women enrolled delivered at a facility, compared with less than 20% of deliveries for the three south Asian studies.[5–7] By contrast with the predominantly rural locations in south Asia, the study site in Southern Province included a mixture of rural and urban sites. In Zambia, only 7% of chlorhexidine and 11% of dry cord care groups had applied non-study substances (eg, breastmilk, baby powder, charcoal, dust) to the cord. In the south Asia studies,[6,7,20] 50–90% of the children in Nepal and Pakistan had additional non-study substances placed on the cord, including mustard oil and coal. In our qualitative research completed before trial initiation, mothers, grandmothers, and health workers described alternative cord application substances and cultural neonatal care practices.[8] However, the newborn baby care messaging that was provided to all ZamCAT study participants could have reduced such alternative cord applications and increased the number of infants who received actual dry cord care. Additionally, only 7% of ZamCAT infants were of low birthweight compared with nearly a third of those in the Nepal[5] and Bangladesh[7] studies.

In view of the different contexts (community *vs* facility delivery, low neonatal mortality rate *vs* high neonatal mortality rate, and cultural practices of cord care) of the south Asian trials compared with those undertaken in sub-Saharan Africa, a rigorous meta-analysis of all the major trials of chlorhexidine cord care is needed, with careful attention paid to weighting of the studies in the meta-analysis, quality scoring, and other related statistical details. Ideally, this meta-analysis should be done under the coordination of an independent objective party. The results of this analysis will be of crucial importance to the development of revised WHO guidelines for umbilical cord care in resource-limited countries.

WHO's guidelines[10] recommend use of chlorhexidine if an infant is delivered at home in environments with a high neonatal mortality rate (≥30 deaths per 1000 livebirths). Rolling out chlorhexidine to all low-income and middle-income settings risks the misuse of resources—time, money, political capital, and, most importantly, patient trust. Simple, evidence-based solutions exist to reduce neonatal mortality in resource-limited settings—skilled birth attendants, neonatal resuscitation, access to basic and comprehensive emergency obstetric care, postnatal visits, kangaroo mother care, early detection and appropriate management of neonatal sepsis, provision of clean delivery kits, clean dry cord care, and exclusive breastfeeding can substantially reduce neonatal mortality.[4,24] Although chlorhexidine is potentially beneficial in places with a high neonatal mortality rate and home-based delivery environments in south Asia, the treatment had no effect on neonatal mortality in Zambia, an environment with a lower neonatal mortality rate, more facility-based deliveries, and with representation of both urban and rural sites. On the basis of these findings, we believe chlorhexidine should not be globally implemented, especially in moderate neonatal mortality environments in Africa.

Contributors

As the co-principal investigators, KEAS and DHH conceived the research question, designed the trial, and oversaw study implementation. KEAS and DHH were responsible for the data analysis, and the writing and revision of the report. KM, RM, PC-K, and GB oversaw completion of the study and participated in study coordination provincially and nationally. BB, CM, FH, and PP worked in the six districts, acquired the data during the initial study phases, supervised the field monitors at the 90 health centres for appropriate study implementation and data collection, and assisted with writing of the report. AZ was the data manager for the field office in Choma and participated in data analysis and writing of the report. KY-A, DMT, and JLS assisted with development of the study design, data analysis, data interpretation, and writing of the report. KEAS and WBM did the data analysis, and wrote the methods, tables, and results. JH and CG were responsible for study oversight, training of study staff, study implementation, and writing of the report. All authors read and approved the final manuscript.

Declaration of interests

All authors received funding from the Bill & Melinda Gates Foundation. We declare no other competing interests.

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