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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 facility-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. 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. Neonatal sepsis and prematurity have emerged as principal challenges to further reductions in neonatal mortality.

Chlorhexidine cord washes have been evaluated as a strategy to reduce umbilical cord infections, sepsis, and neonatal mortality. Although three previous studies found that topical chlorhexidine umbilical cord wash 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.

Dry cord care has been the long-standing recommendation of umbilical cord care for most newborn babies. Updated WHO guidelines recommend application of chlorhexidine to the umbilical stump...
Research in context panel

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 RRmeta 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.

Methods
Study design
We did a community-based, cluster-randomised con-
trolled 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%.[9] The design and methods of ZamCAT have been reported elsewhere.[9] 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.

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. 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 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.

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

90 clusters randomly assigned

45 clusters assigned to chlorhexidine group

21 280 pregnant women screened

630 excluded

45 clusters assigned to dry cord care group

21 044 pregnant women screened

617 excluded

19 629 women enrolled

18 639 women had 18 958 deliveries

348 stillbirths

18 530 livebirths

19 492 women had 19 721 deliveries

375 stillbirths

19 346 livebirths

86 neonates excluded

82 neonatal deaths

4 lost to follow-up

0 withdrew

80 neonates excluded

77 neonatal deaths

3 lost to follow-up

0 withdrew

123 neonates excluded

109 neonatal deaths

8 lost to follow-up

6 withdrew

101 neonates excluded

93 neonatal deaths

7 lost to follow-up

1 withdrew

57 neonates excluded

45 neonatal deaths

10 lost to follow-up

2 withdrew

38 neonates excluded

33 neonatal deaths

4 lost to follow-up

1 withdrew

18 244 neonates alive at day 1 follow-up

13 921 day 1 follow-up visits

18 301 neonates alive at day 4 follow-up

17 876 day 4 follow-up visits

18 266 neonates alive at day 1 follow-up

18 937 day 1 follow-up visits

19 165 neonates alive at day 4 follow-up

18 816 day 4 follow-up visits

18 450 neonates included in analyses

19 045 neonates alive at day 28 follow-up

18 968 day 28 follow-up visits

19 308 neonates included in analyses
| Chorhexidine (n=19 629) | Dry cord care (n=20 050) |
|------------------------|--------------------------|
| **Age**                |                          |
| <20 years              | 4672 (24.0%)             |
| 20−35 years            | 12 772 (65.6%)           |
| >35 years              | 2012 (10.3%)             |
| Median household size (IQR) | 6 (4–8)               |
| **Woman's highest level of education** |                   |
| No education           | 1936 (9.9%)              |
| Lower primary (grade 1-4) | 2293 (11.8%)   |
| Upper primary (grade 5-7) | 7731 (39.7%)           |
| Junior secondary (grade 8-9) | 5422 (27.9%)       |
| Upper secondary (grade 10-12) | 1895 (9.7%)         |
| >Upper secondary       | 180 (0.9%)               |
| **Ethnic origin or tribe** |                   |
| Tonga                  | 17 003 (87.4%)           |
| Ilu                    | 105 (0.5%)               |
| Lozi                   | 786 (4.0%)               |
| Nyanja                 | 525 (2.7%)               |
| Bemba                  | 413 (2.1%)               |
| Other                  | 629 (3.2%)               |
| **Marital status**     |                          |
| Single                 | 3021 (15.5%)             |
| Married                | 16 107 (82.8%)           |
| Separated, divorced, or widowed | 224 (1.2%) |
| Cohabiting             | 109 (0.6%)               |
| Missing                | 2 (0.01%)                |
| **Maternal literacy ability** |                   |
| Not at all             | 5037 (25.9%)             |
| A bit                  | 8835 (45.4%)             |
| Very well              | 5492 (28.2%)             |
| No response            | 77 (0.4%)                |
| **Household water source** |                     |
| Household tap          | 1861 (9.6%)              |
| Community tap          | 1715 (8.6%)              |
| Other water source on own property | 2295 (11.8%) |
| Community well or river | 13 241 (68.1%)        |
| No answer              | 56 (0.3%)                |
| Other                  | 67 (0.3%)                |
| **Housing roof type**  |                          |
| Iron sheets or asbestos | 8854 (45.7%)            |
| Thatched grass         | 10 462 (53.3%)           |
| Do not know            | 36 (0.2%)                |
| Other                  | 42 (0.2%)                |
| **Housing wall materials** |                     |
| Cement bricks without plaster | 763 (3.9%)        |
| Cement bricks with plaster | 2017 (10.4%)        |
| Other bricks without plaster | 12 780 (65.7%)   |
| Other bricks with plaster | 2608 (13.4%)   |
| Mud and poles          | 1196 (6.2%)              |
| **Time walking from home to health facility** |                   |
| <1 h                   | 6404 (33.0%)             |
| 1 h to <2 h            | 6854 (35.3%)             |
| 2 h to <3 h            | 4179 (21.5%)             |
| 3 h to <4 h            | 1425 (7.3%)              |
| 4 h to <5 h            | 284 (1.5%)               |
| ≥5 h                   | 212 (1.1%)               |
| **Parity**             | 2.4 (2.3)                |
| **Gravida**            | 3.5 (2.3)                |
| Had a previous child die in neonatal period | 3536 (18.3%) |
| Gestational age at enrolment based on LMP (weeks) | 28 (0.7) |
| Bed net previous night* | 11 092/19 402 | 11 783/19 858 |

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

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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.7

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.8 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,1 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 $\alpha=0.05$), 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-analysis9 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.10 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, 

| Antenatal visits attended | Chlorhexidine (n=18 510) | Dry cord care (n=19 346) |
|--------------------------|-------------------------|-------------------------|
| Male infant              | 3 3 (0 0)               | 3 4 (0 0)               |
| 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) | 348/16 763 (20 8%) | 352/17 286 (20 4%) |

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

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

| 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 24-48 h of birth | 17 815 (96.2%) |
| No chlorhexidine application | 396 (2.1%) |
| One application of chlorhexidine | 60 (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 | 16 99 (9.2%) |
| Participant follow-up | 2450 (12.7%) |

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

Data are n (%), or mean (SD). *Of 57 332 infants. \( \text{Denominator is } 18 301 \text{ infants in the chlorhexidine group and } 19 165 \text{ in the dry cord care group.} \) \( \text{Denominator is } 18 244 \text{ infants in the chlorhexidine group and } 19 127 \text{ in the dry cord care group.} \) \( \text{Denominator is } 18 168 \text{ infants in the chlorhexidine group and } 19 045 \text{ in the dry cord care group.} \)

Baseline characteristics potentially associated with the outcomes were compared between the two groups using appropriate tests. Variables were compared between groups using the \( \chi^2 \) 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).\(^{10} \text{41110} (97.0\%) \text{ 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...
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 37800 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). 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, 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.

Table 4: Neonatal mortality by study group

| 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 | 1.00 (0.86–1.17) |
| Chlorhexidine | 18 510 | 282 | 15.2 | 1.12 (0.88–1.44) |
| (48.9%) | (51.7%) | | |
| Dry cord care | 19 346 | 263 | 13.6 | 0.94 (0.72–1.22) |
| (51.1%) | (48.3%) | | |
| All-cause neonatal mortality (excluding day 0 deaths) | | | |
| All livebirths who survived day 0 | 37 690 | 386 | 10.2 | 1.00 (0.77–1.28) |
| Chlorhexidine | 18 424 | 200 | 10.9 | 1.12 (0.86–1.47) |
| (48.9%) | (51.8%) | | |
| Dry cord care | 19 266 | 186 | 9.7 | 0.88 (0.66–1.16) |
| (51.2%) | (48.2%) | | |

**As practised analysis**

| All-cause neonatal mortality (excluding day 0 deaths) | | | |
| All livebirths | 35 871 | 327 | 9.11 | 1.00 (0.78–1.27) |
| Chlorhexidine | 16 645 | 141 | 8.5 | 0.88 (0.66–1.16) |
| (50%) | (14%) | | |
| Dry cord care | 19 266 | 186 | 9.7 | 0.88 (0.66–1.16) |
| (51%) | (16%) | | |

Propensity-score analysis (excluding day 0 deaths)

| Chlorhexidine | 16 400 | 132 | 8.0 | 0.94 (0.72–1.22) |
| (50%) | (8%) | | |
| Dry cord care | 16 400 | 141 | 8.6 | 0.90 (0.69–1.16) |
| (50%) | (9%) | | |

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

**Birthweight (n=23 422)**

| Livebirths | Neonatal deaths | NMR per 1000 livebirths | Relative risk* (95% CI) |
|------------|----------------|--------------------------|------------------------|
| Low birthweight (>2 500 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 (≥2 500 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=34 029)**

| Livebirths | Neonatal deaths | NMR per 1000 livebirths | Relative risk* (95% CI) |
|------------|----------------|--------------------------|------------------------|
| Premature (<37 weeks) | | | |
| Chlorhexidine | 3 484 (10.2%) | 111 (0.3%) | 31.9 | 1.03 (0.74–1.44) |
| Dry cord care | 3 521 (10.3%) | 105 (0.3%) | 31.0 | - |
| Normal gestational age (≥37 weeks) | | | |
| Chlorhexidine | 12 269 (30.9%) | 125 (0.4%) | 10.2 | 1.16 (0.86–1.59) |
| Dry cord care | 13 165 (40.4%) | 120 (0.4%) | 8.7 | - |

**Maternal HIV status known (n=36 593)**

| Livebirths | Neonatal deaths | NMR per 1000 livebirths | Relative risk* (95% CI) |
|------------|----------------|--------------------------|------------------------|
| Infant exposed to HIV (n=21 013) | | | |
| Chlorhexidine | 1 631 (52.6%) | 38 (1.2%) | 23.2 | 1.14 (0.62–2.11) |
| Dry cord care | 1 472 (47.4%) | 30 (1.0%) | 20.4 | - |
| Infant not exposed to HIV (n=13 400) | | | |
| 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)**

| Livebirths | Neonatal deaths | NMR per 1000 livebirths | Relative risk* (95% CI) |
|------------|----------------|--------------------------|------------------------|
| 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 | 6 698 (49.6%) | 97 (0.7%) | 14.2 | 1.25 (0.86–1.83) |
| Dry cord care | 6 809 (50.4%) | 77 (0.6%) | 11.3 | - |

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

Table 5: Neonatal mortality by pre-specified health indicators

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 in south Asia comparing chlorhexidine cord washes to dry cord care. A cluster-randomised trial in Nepal 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 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. Finally, in rural Pakistan, daily chlorhexidine cord applications resulted in significant reductions in neonatal mortality and omphalitis. All three studies 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. 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. Important differences exist between the observed incidence of omphalitis and the meta-analysis which did not include the data from the Bangladesh study.
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. 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, 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. 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 Nepal1 and Bangladesh1 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 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. Although chlorhexidine is potentially beneficial in places with a high neonatal mortality rate and home-based delivery environments in 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. XM, RM, PC-R, 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. KYA, 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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References
1 You D, Wardlaw T, Newby H, Anthony D, Rogers K. Renewing the promise of survival for children. Lancet 2011; 382: 1002–04.
2 Lawn JE, Blencowe H, Oza S, et al, for The Lancet Every Newborn Study Group. Every Newborn: progress, priorities, and potential beyond survival. Lancet 2014; 384: 189–205.
3 Liu L, Oza S, Hogan D, et al, for Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015; 385: 430–40.
4 Bhutta ZA, Das JK, Bahl R, et al, for The Lancet Newborn Interventions Review Group, The Lancet Every Newborn Study Group. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? Lancet 2014; 384: 347–70.
5 Mullyan LC, Darmstadt GL, Khatry SK, et al. Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomised trial. Lancet 2006; 367: 910–18.
6 Soofi S, Cousens S, Imdad A, Bhutto N, Ali N, Bhutta ZA. Topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, cluster-randomised trial. Lancet 2012; 379: 1029–36.
7 Arifeen SE, Mullyan LC, Shah R, et al. The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster-randomised trial. Lancet 2012; 379: 1022–28.
8 Herlihy J, Shaikh A, Mazimba A, et al. Local perceptions, cultural beliefs and practices that shape umbilical cord care: a qualitative study in Southern Province, Zambia. *PLoS One* 2013; 8: e79191.

9 WHO. Care of the umbilical cord: a review of the evidence. Geneva: World Health Organization, 1998.

10 WHO. WHO recommendations on postnatal care of the mother and newborn. Geneva: World Health Organization; 2014.

11 USAID. Chlorhexidine technical brief: umbilical cord cleansing with 4% chlorhexidine saves newborn lives. Washington DC: USAID, 2012.

12 Sazawal S, Dhirgra U, Ali SM, et al. Efficacy of chlorhexidine application to umbilical cord for the first 7 days of life on neonatal mortality and omphalitis in Pemba, Tanzania: a community-based randomised controlled trial. *Lancet Glob Health* 2016; published online Sept 29. http://dx.doi.org/10.1016/S2214-109X(16)30223-6.

13 Central Statistical Office, Zambia Ministry of Health, Tropical Diseases Research Centre, University of Zambia, and Macro International Inc. Zambia demographic and health survey 2007. Calverton, MD: Central Statistical Office and Macro International Inc, 2009.

14 Hamer DH, Herlihy JM, Musokotwane K, et al. Engagement of the community, traditional leaders, and public health system in the design and implementation of a large community-based, cluster-randomized trial of umbilical cord care in Zambia. *Am J Trop Med Hyg* 2013; 92: 666–72.

15 Zambian Ministry of Health. Pregnancy, Childbirth, Postpartum and Newborn Care Guidelines: a guide for essential practice in Zambia. Lusaka: Zambian Ministry of Health, 2008.

16 Zambian Ministry of Health. 2010 national protocol guidelines: integrated prevention of mother-to-child transmission of HIV. Lusaka: Zambian Ministry of Health, 2010.

17 Hayes RJ, Moulton LH. Cluster randomised trials. Boca Raton: CRC Press, 2009.

18 Owens I, Semrau K, Mbeewa R, et al. The state of routine and emergency obstetric and neonatal care in Southern Province, Zambia. *Int J Gynaecol Obstet* 2015; 128: 53–57.

19 Imdad A, Mullany LC, Baqui AH, et al. The effect of umbilical cord cleansing with chlorhexidine on omphalitis and neonatal mortality in community settings in developing countries: a meta-analysis. *BMC Public Health* 2013; 13: S15.

20 Mullany LC, Darmstadt GL, Khatri SK, LeClerq SC, Katz J, Tielsch JM. Impact of umbilical cord cleansing with 4–0% chlorhexidine on time to cord separation among newborns in southern Nepal: a cluster-randomized, community-based trial. *Pediatr* 2006; 118: 1864–71.

21 Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012; 379: 2151–61.

22 Oestergaard MZ, Inoue M, Yoshida S, et al. Neonatal mortality levels for 193 countries in 2009 with trends since 1990: a systematic analysis of progress, projections, and priorities. *PLoS Med* 2011; 8: e1001080.

23 Lawn JE, Kinney MV, Black RE, et al. Newborn survival: a multi-country analysis of a decade of change. *Health Policy Plan* 2012; 27 (suppl 3): i16–28.

24 Seward N, Osrin D, Li L, et al. Association between clean delivery kit use, clean delivery practices, and neonatal survival: pooled analysis of data from three sites in South Asia. *PLoS Med* 2012; 9: e1001180.