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A Randomized Controlled Trial of Chlorhexidine Vaginal and Infant Wipes to Reduce Perinatal Mortality and Morbidity

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Abstract

Background—Sepsis is a leading cause of perinatal death in developing countries. Vaginal organisms acquired during labor play a significant role. Prior studies suggest that chlorhexidine wiping of the maternal vagina during labor and of the neonate may reduce peripartum infections.

Methods—We performed a placebo-controlled, randomized trial of chlorhexidine vaginal and neonatal wipes to reduce neonatal sepsis and mortality in three hospitals in Pakistan. The primary study outcome was a composite of neonatal sepsis or 7-day perinatal mortality.

Findings—From 2005 to 2008, 5,008 laboring women and their neonates were randomized to receive either chlorhexidine wipes (n = 2,505) or wipes with a saline placebo (n = 2,503). The primary outcome was similar in the chlorhexidine and control groups, (3.1% vs. 3.4%; RR 0.91, 95% CI 0.67, 1.24), as was the composite rate of neonatal sepsis or 28-day perinatal mortality, (3.8% vs. 3.9%, RR 0.96, 95% CI 0.73, 1.27). At day 7, the chlorhexidine group had a lower rate of neonatal skin infection. (3.3 vs. 8.2%, p<0.0001) With the exception of less frequent 7-day hospitalization in the chlorhexidine group, there were no significant differences in maternal outcomes between the groups.

Interpretation—This trial provides evidence that the use of maternal chlorhexidine vaginal wipes during labor and neonatal chlorhexidine wipes does not reduce maternal and perinatal mortality or neonatal sepsis. The finding of reduced superficial skin infections on day 7 without change in sepsis or mortality suggests that this difference, although statistically significant, may not be of major importance.

Trial Registration: Clinicaltrials.gov: NCT00121394

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INTRODUCTION

In many developing countries, pneumonia and sepsis are the major causes of neonatal mortality.(1,2) The organisms causing neonatal infection in developing countries are generally Gram negative (*Klebsiella pneumoniae* and *Escherichia coli*), whereas group *B streptococci* is often the organism causing neonatal sepsis in developed countries.(1) These organisms likely originate in the maternal genital tract and are transmitted to the fetus during labor and delivery. Decreasing mother to infant transmission of these organisms has been advocated as a potential approach to reducing perinatal infections.

It has been proposed that periparturient infection of the fetus and mother may be prevented by intrapartum vaginal and neonatal wipes with an antiseptic solution.(3,4) One such antiseptic solution is chlorhexidine which has a wide range of effectiveness against aerobic and anaerobic Gram negative and Gram positive organisms. In an attempt to reduce neonatal infections, vaginal chlorhexidine, variously applied and in varying strengths, has been tested as a means to reduce perinatal infections. Chlorhexidine acetate, diacetate, gluconate and digluconate solutions have been used in concentrations ranging from 0.25 % to 0.5% and at these concentrations are essentially free of side effects.(5) However, concentrations of 1% or greater are associated with increased vaginal burning and itching.(6)

Several studies in Scandinavia showed reduced neonatal bacterial colonization following chlorhexidine vaginal wiping. However, the results of studies in developed countries, with neonatal sepsis endpoints, were inconsistent.(7–11) Developing country quasi-randomized studies showed more promise. Taha et al in Malawi and Bakr et al in Egypt both appeared to show that 0.25% chlorhexidine vaginal and neonatal wiping reduced neonatal deaths due to sepsis and improved a number of other neonatal and maternal outcomes.(12,13) In a subgroup analysis of a community based study conducted in Nepal, neonatal wiping with 0.25% chlorhexidine wiping was associated with a reduction in mortality only among low birth weight infants.(14) A recently published randomized study showed no maternal or neonatal benefit.(5)

Because of the potential for chlorhexidine vaginal and baby wipes to reduce perinatal infections, because a small pilot study in Karachi suggested possible benefits in reducing newborn infections(15) and because of the methodological shortcomings of some prior studies, we conducted a hospital-based placebo controlled randomized trial of chlorhexidine vaginal and baby wipes to evaluate their impact on fetal/neonatal mortality and infection-related morbidity. For the wipes, we used a strongly bacteriocidal (0.6%) chlorhexidine solution and compared the outcomes to those seen with wipes in a control group that received normal saline.

METHODS

Between June 13, 2005 and May 27, 2008, three public hospitals that provide services to the poor, urban population of Karachi, Pakistan participated in this study. Civil Hospital Karachi is affiliated with Dow University of Health Sciences, and the remaining two hospitals are affiliated with the provincial and city governments. We had two separate types of teams for the study. The hospital study teams of doctors and nurses were trained on study screening, randomization and enrollment procedures, performing the vaginal and baby wipes, and data collection 24 hours a day and 7 days a week. The field teams also consisted of doctors and nurses; they were trained to conduct follow-up home visits at day 7 and 28 in which they examined mothers and neonates and collected study data. Each team worked independently of the other and both were masked to treatment allocation.

Women 18 to 45 years of age who were admitted to deliver in any of the study hospitals were screened for eligibility to participate in the study. Women were excluded from the study if they had a contraindication to digital cervical exam (e.g., placenta previa), active genital herpes, vulvovaginal ulceration, face presentation, known fetal death, known or suspected allergy to chlorhexidine, a planned cesarean section, arrived late in labor with full cervical dilatation, who were from troubled areas of Karachi where follow up was risky, or were unwilling or unable to give consent. If an enrolled woman had twins, only the first born received the intervention and was counted as a study participant.

Commercially-available chlorhexidine diacetate powder was purchased from Degussa (Germany). The research pharmacist at the Aga Khan University (AKU) prepared the 0.6% solution using sterile water (7.14 gm per litre). The solution was buffered to pH 8 with the addition of hydrochloric acid, and in 4 sterile 100 ml amber colored bottles, packed in a cardboard box. Sterile saline solution in identical bottles and boxes served as the placebo.

Randomization and masking

The data center (Research Triangle Institute [RTI], US) prepared a randomization list for each of the three hospitals, with random treatment allocation generated in blocks of 4 and 8. Since both solutions were clear and odorless, neither the study team members nor the subjects could differentiate between the two. The assignment of the women to the study group was accomplished through the study solution pack prepared according to the randomization list by the hospital pharmacist, who was the only person with access to the randomization assignment. Each hospital maintained study solutions in a designated area and study solutions were used in sequential order. Two separate sterilized packs of gloves, plastic trays, and cotton balls for application of study solution to the neonate and mother were also provided. The study solution was warmed before use in a closed container in a water bath where temperature was monitored so as not to exceed 37°C. The vaginal wipe was performed by the study doctor or nurse once the woman was deemed to be in labor and then every 4 hours (up to 3 times maximum) until delivery. Using sterile gloves, a study-solution-soaked cotton ball was rotated by the fingers in a circumferential manner to cover the entire cervix, the vagina, and the external genitalia. Every enrolled woman received a minimum of one wash at least an hour before the delivery of the baby. The neonate (excluding the head and face) was wiped with 100 mL of study solution, usually immediately after delivery, but always within 6 hours of birth, by the hospital study team staff. To preserve the vernix, the team was instructed to gently pat the newborn, and then to prevent hypothermia, immediately dry and wrap the neonate. Labor room staff was instructed to not to bathe the neonates of mothers enrolled in the study before the study solution wipe.

To ensure that the women were receiving the treatment to which they were assigned and that the concentration of chlorhexidine was appropriate and bacteriocidal, tests were performed on randomly chosen bottles by an independent laboratory. These tests confirmed that bottles presumed to contain chlorhexidine solution did so and in a concentration of 0.6%. Additionally, they were bacteriocidal, while the bottles presumed to contain saline had no detectable chlorhexidine and were not bacteriocidal.

The primary study outcome was the composite of fetal and neonatal mortality and neonatal sepsis on or before day 7 of life. Any fetal deaths occurring during delivery were included in the final analysis as the fetuses were alive at enrollment and this was an intent-to-treat trial. Sample size calculations indicated that a trial of 5000 women, with 2500 in each treatment group, would have 80% power (two-tailed test at $\alpha=0.05$) to detect a difference between a control group primary outcome rate of 52 per 1000 births and the corresponding primary outcome rate of 35 per 1000 in the chlorhexidine group. Secondary outcomes included

neonatal sepsis or mortality on or before day 28, maternal mortality on or before 28 days, and various measures of infection-related morbidity including hospital admission or re-admission.

Women were asked to identify any symptoms of burning, itching, rash or redness and to quantify the severity of these symptoms using a visual analogue scale which had been pre-tested in a Pakistani population.(15) All infants were examined by the physicians within a half hour of the infant wipe to assess any symptoms of rash, redness, tenderness and swelling.

Newborns with Apgar Scores of less than 7 at one and five minutes were referred to the respective neonatal intensive care units (NICUs) of the study hospitals and study wipes were given only after the approval of the attending physician. The admitted newborns were followed daily until the primary outcome (i.e., discharged alive, remained admitted until day 7 and 28 or death occurred.) The relevant information regarding diagnosis by the attending physician, laboratory tests, and X-rays (where available) was retrieved from the hospital records.

At the day 7 and day 28 visits, study physicians assessed both the mother and infant for illness. For infants, the IMCI screening tool (16) for identification of severe illness in young infants was used. The IMCI screening tool, which has been validated in research studies, includes a checklist of clinical signs of severe infection.(17) Presence of at least 3 clinical signs and one severe symptom must be present in order to be classified as positive for sepsis. In addition, identification of skin and umbilical infections was performed by visual examination of the infant as well as by showing pictures of infant skin infections to mothers and were graded using standardized criteria. (All infants were examined for skin infections on day 7 and 28, and a sub-group of 1412 consecutively born infants were examined on day 14.) Mothers were questioned about fever, lower abdominal pain, and vaginal discharge. Referrals to the hospital were made as appropriate according to IMCI criteria and the maternal condition. Whenever possible, neonates or mothers who entered a hospital were followed-up at the hospital to retrieve appropriate information. Maternal and infant discharge summaries with diagnoses and laboratory reports were examined.

For the screening for infection using IMCI and for identification of skin and umbilical infections, the study team was trained by a neonatologist by demonstrating the examination on neonates in neonatal wards of these tertiary hospitals. A trainer from the study team provided additional training and observed the other team members during data collection and for random quality checks. Repetitive training was provided throughout the trial.

A panel of three neonatologists and one obstetrician gynecologist who were not members of the study team reviewed records of the neonates 1) who were admitted to the NICUs after delivery, 2) who were readmitted until day 28 after discharge from hospital, or 3) were referred to the hospital by the study team because of potential severe illness. Records of neonates receiving antibiotics prescribed by a local general practitioner were also reviewed. Along with the neonatal information, maternal events at the time of delivery were also reviewed including highest temperature, meconium stained amniotic fluid, foul smelling vaginal discharge, purulent vaginal discharge, tender uterus/abdomen, clinical diagnosis of chorioamnionitis (physician opinion), clinical diagnosis of urinary tract infection (physician opinion), duration of labor pains, and duration of membrane rupture. Based on their overall judgment of the clinical and laboratory data, and maternal events at the time of delivery, the panel classified each case into the following categories.

- a. Sepsis: Infants identified as severely ill by IMCI screen or clinical presentation, maternal history and involvement of at least one organ system and lab findings

- b. Probable sepsis: Infants identified as severely ill by IMCI screen, clinical presentation, and had a maternal history supporting infection
- c. Possible sepsis: These infants were severely ill by IMCI screen or clinical screen and had no evidence of a non-septic condition to account for their condition
- d. Not sepsis: These infants were screened as ill by IMCI screen, had no evidence of infection on clinical screen and usually had evidence of another condition to account for their condition.

Infants who were classified as having sepsis, probable sepsis or possible sepsis were classified as “sepsis” for analyses of the primary outcome.

All completed forms were edited by the field supervisor (a doctor) immediately after completion of the data forms at the hospital so that any discrepancies or missing information could be corrected in a timely manner. These forms were further edited by a data entry supervisor before entry into the study data management system. Data were transmitted to the data center where inter and intra-form edits were performed.

Data were analyzed using the intent-to-treat principle with SAS 9.1.3 (SAS Institute Inc, US). Descriptive statistics (frequencies, percentages, means, standard deviations and relative risks and 95% confidence intervals) were calculated, excluding missing data from the analyses. Participants with missing outcomes due to loss to follow-up were excluded from the analyses of outcomes. In the case of twin pregnancies, only the outcome of the firstborn was included and analyzed because the outcomes of twin pairs are correlated with each other. Comparisons between the chlorhexidine and placebo groups were performed using chi-square tests for binary outcomes and t-tests for continuous outcomes. In the case of sparse binary outcomes, Fisher’s exact tests were computed. P-values were not adjusted for multiple comparisons. Relative risks and their 95% confidence intervals were used to estimate the association between chlorhexidine and placebo wash with maternal and neonatal outcomes.

Ethical approvals from the all the participating institutions were obtained. The Data Monitoring Committee met every six months and monitored the trial throughout. None of the authors had a conflict of interest.

RESULTS

Figure 1 shows study enrollment, randomization and follow-up: 20,800 women were screened from 2005 to 2008. About 63% of the screened women were not eligible for the study and excluded (n=13,100). About 37% of these women were excluded because their admission was for elective cesarean section and 27% were excluded because they were fully dilated upon arrival at the hospital. Another 26% of the women were excluded because they did not live in the study catchment area. In addition, some women (4.4%) arrived at the hospital with a known fetal death. Finally, women who had conditions that contraindicated a cervical examination (2.2%) were excluded. Thus 7,700 of the women screened were eligible for the study. Of those, about 35% refused consent, often because accompanying family members did not give permission in the husbands’ absence. A total of 5,008 women were randomized.

The treatment and control groups were similar regarding maternal age, gravidity, number of living children, abortions, gestational age at delivery, labor duration, percent with a twin pregnancy or cesarean section, and type of membrane rupture. (Table 1) There were also no statistically significant differences in gestational age at delivery and infant mean birth weight or birth weight distribution, Apgar Scores and the gender distribution. Of the mothers

randomized to chlorhexidine, 99.8% received at least one wipe, as did 99.9% of those randomized to placebo. The respective percentages for infants were 98.3% and 98.8%. The mean number of maternal wipes was 1.2 and was similar between the treatment groups.

There were no major maternal or newborn complications including death, anaphylactic shock, toxic epidermal necrolysis syndrome (Stevens-Johnson Syndrome), generalized urticaria, or necrotizing fasciitis related to chlorhexidine use. Women who received chlorhexidine had more itching and burning than those who received the saline placebo wipe while those infants who received chlorhexidine had less rash and skin redness. (Table 2) None of these findings persisted for more than one hour and none resulted in any obvious sequelae.

A total of 1596 cases (32%) of sick neonates were reviewed by the panel for the assignment of primary outcome. There was not a significant difference between the chlorhexidine and placebo groups in the primary study outcome of neonatal death or neonatal sepsis within seven days of birth, nor in the separate components of this outcome. (Table 3) Neonatal sepsis rates were not different between the groups, nor was overall perinatal mortality (including stillbirths). Prospectively defined secondary neonatal outcome rates, including 28-day neonatal sepsis or mortality (analyzed as a composite or as separate component) were also not different. The mean number of infant hospital days prior to discharge was similar in both groups (data not shown) as were the number of infants remaining in the hospital at day 7 or re-hospitalized prior to day 28 of life. (Table 3)

The percentage of neonates having a skin infection prior to or on day 7 was less in the chlorhexidine group compared to placebo group, 3.3% vs. 8.2%, respectively, $p<0.0001$. (Table 4) Both bullous and pustular infections were decreased in the chlorhexidine compared to placebo group on day 7. However, at days 14 and 28, the rates of skin infection were not significantly different for chlorhexidine vs. the placebo group.

Maternal deaths were rare and did not differ significantly between the groups. (Table 5) Rates of purulent or foul-smelling vaginal discharge or a tender uterus prior to day 7 or within the first 28 days were also similar between groups. The only statistically significant difference between the groups was fewer mothers hospitalized at day 7 in the chlorhexidine group. The decrease in this outcome in the chlorhexidine group was partially explained by fewer infected Cesarean section wounds and episiotomies, as well as lower rates of maternal fever (data not shown).

As the trial progressed, we became aware that peripartum antibiotic use in the three study hospitals was very common, and collected antibiotic usage data after about 600 women were randomized. Of the 4,378 women for whom we have these data, 594 in the chlorhexidine group and 592 in the placebo group received no antibiotics, 246 in the chlorhexidine group and 236 in the placebo group received intrapartum antibiotics and 1,352 women in the chlorhexidine group and 1,358 in the placebo group received only post-partum antibiotics. To test whether chlorhexidine was effective in reducing the rate of the primary outcome among neonates born to women who did not receive antibiotics during labor, a sub-analysis was performed in the combined group of mothers who received no antibiotics or only post-partum antibiotics. There was no difference in the primary outcome between the groups (3.0% chlorhexidine vs. 3.1% placebo, $p=0.85$)

Because a previous study suggested potential benefit of chlorhexidine for low birth weight infants,(13) the various primary and secondary outcomes were stratified by birth weight. Categories of <2000 grams, 2000 – 2500 g and >2500 grams were evaluated. No statistically significant differences were found between the chlorhexidine and placebo groups in any outcome in any birth weight group (data not shown).

DISCUSSION

This trial from a developing country provides little evidence that the use of a combination of maternal chlorhexidine vaginal wipes during labor and neonatal wipes applied soon after birth reduces maternal and neonatal sepsis when compared with normal saline wipes. These findings are in contrast to two large non-randomized developing country studies that suggested an improvement in a number of infection-related perinatal outcomes in the chlorhexidine arms. (12,13) However a recent randomized trial conducted in South Africa did not show a beneficial effect of chlorhexidine vaginal and baby wipes in prevention of neonatal sepsis or the vertical transmission of potentially pathogenic bacteria among neonates, supporting our findings. (5)

The randomized trials of vaginal and neonatal chlorhexidine wipes published to date from developed countries.(8–11) and now one from South Africa, have not shown benefit in reducing neonatal sepsis or mortality. To maximize the potential effectiveness of the intervention, we thought it worthwhile to increase the concentration of chlorhexidine to more than double the concentration used in most previous studies. However, despite this higher concentration, chlorhexidine had no impact on neonatal sepsis or mortality in our trial. As in developed countries, there is now strong evidence that this intervention does not contribute to the solution of the important problem of neonatal sepsis.

The reduction in neonatal skin infections on day 7 was statistically significant and by its magnitude, likely to be real. The result is also plausible in that a preventive treatment at birth would be expected to show a reduction in early but not late skin infections. However, this difference in skin infections did not manifest itself in a reduction of mortality, sepsis or other measures of maternal morbidity such as hospital length of stay or increased readmissions. Without a clear improvement in these measures, it is difficult to recommend the use of perinatal chlorhexidine washes simply to reduce superficial skin infections not associated with increased morbidity. A large community based trial in Nepal of neonatal skin cleansing with 0.25% chlorhexidine did not show a reduction in mortality in all neonates treated.(14) However, in a secondary analysis, a significant reduction in mortality was observed in low birth infants. Our trial did not show any trend toward a reduction in either sepsis or mortality in low birth weight neonates in the chlorhexidine group. A large study of repetitive umbilical cord wiping over 10 days with 4% chlorhexidine found neonatal benefit.(18) The results of our trial should not affect the interpretation of those results.

In carrying out this study, we used a validated set of criteria (IMCI) to screen neonates for severe illness.(16,17) At the completion of the trial, but prior to breaking the randomization code, a panel of three neonatologists reviewed all adverse outcomes possibly related to neonatal sepsis to arrive at a study endpoint of neonatal sepsis. This outcome together with death comprised our final study endpoint. Neonatal death can be caused by conditions other than sepsis such as asphyxia, but since it is difficult to distinguish between these two diagnoses, even in settings with sophisticated laboratory and pathologic resources including autopsy, we chose to include neonatal deaths from any cause as part of our primary endpoint. The combined rate of sepsis and death was lower than expected, but because there was not even a trend toward a reduction in mortality or sepsis in the treatment group, this finding suggests that even if the primary outcome rate were higher, there would have been no significant difference in outcome.

With the exception of the number of maternal admissions at day seven, there were also no apparent benefits to the *mother* from the vaginal chlorhexidine wipes. While the reduction in hospital admissions in the chlorhexidine group may have been a chance occurrence, it is

possible that vaginal cleansing with chlorhexidine resulted in fewer genital and wound infections due to vaginal organisms. Bakr et al also reported fewer hospital admissions in women who were given vaginal wipes in labor with 0.25% chlorhexidine.(13) In our study, none of the other markers of maternal infection were significantly reduced in the chlorhexidine group, and in any case, the reduction in hospital stay affected only 14 additional women and was not associated with a decrease in mortality or other measurable sequelae.

Many of the study women received antibiotics, mostly in the post partum period, but in the intrapartum period as well. It might be postulated that antibiotic use in both study groups may have resulted in the absence of a difference in infection related neonatal and maternal morbidity. However, analyses limited to those women who did not receive intrapartum antibiotics provide no support for this supposition. Cutland et al from South Africa reported no effect of chlorhexidine vaginal and neonatal wipes on sepsis related morbidity in mothers and neonates who generally did not receive antibiotics before delivery.(5)

Despite the failure of chlorhexidine maternal and vaginal wipes to reduce sepsis and mortality, it remains clear that infection is a major cause of neonatal morbidity and mortality in many developing country settings.(19) Strategies that have shown promise in reducing neonatal death from neonatal sepsis once it occurs include antibiotics administered by community health workers as well as various other antibiotic administration strategies.(20) However, other than giving penicillin or similar antibiotics to the mother to prevent Group B streptococcus transfer to the fetus, we are not aware of other strategies that are effective in preventing newborn acquisition of vaginal organisms resulting in neonatal sepsis. For example, in a recent African study of intrapartum antibiotics to the mother in a population of mostly HIV positive women, neonatal mortality and apparent sepsis were not reduced.(21) Thus, it would be important to develop strategies that reduce or prevent newborn bacterial colonization as well as strategies that reduce death once infection occurs.

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Figure 1.
Study Enrollment and Follow-up

Table 1**Maternal and Neonatal Characteristics by Treatment Group**

	Chlorhexidine	Saline placebo	P-value
Mothers randomized, n	2,505	2,503	
Maternal age, mean (SD)	25.3 (4.6)	25.4 (4.6)	0.59
Gravidity, mean (SD)	2.8 (2.0)	2.8 (2.1)	0.68
Number of living children, mean (SD)	1.4 (1.7)	1.5 (1.8)	0.76
Number of abortions, mean (SD)	0.2 (0.6)	0.2 (0.6)	0.29
Duration of labor (hours), mean (SD)	10.2 (10.3)	10.0 (7.2)	0.39
Twin pregnancy, n (%)	38 (1.5)	29 (1.2)	0.27
Type of rupture of membranes, n	2,106	2,146	0.77
Artificial, n (%)	1,249 (59.3)	1,293 (60.3)	
Spontaneous, n (%)	842 (40.0)	840 (39.1)	
Absent, n (%)	15 (0.7)	13 (0.6)	
Type of delivery, n	2,498	2,494	0.73
Spontaneous vaginal, n (%)	2,287 (91.6)	2,290 (91.8)	
C-section, n (%)	211 (8.4)	204 (8.2)	
Infant randomized, n	2,505	2,503	
Gestational age at delivery, mean (SD)	39.3 (2.3)	39.4 (2.8)	0.67
Gestational age at delivery, n	1,566	1,539	0.75
<37 weeks, n (%)	124 (7.9)	126 (8.2)	
37 – 40 weeks, n (%)	1,064 (67.9)	1,026 (66.7)	
> 40 weeks, n (%)	378 (24.1)	387 (25.1)	
Birth weight grams, mean (SD)	2,965.0 (450.7)	2,967.9 (451.3)	
Birth weight, n	2,494	2,486	0.82
<2000 grams, n (%)	25 (1.0)	24 (1.0)	0.95
2000–2500 grams, n (%)	458 (18.4)	465 (18.7)	
>2500 grams, n (%)	2,011 (80.6)	1,997 (80.3)	
Gender, n	2,497	2,488	
Male, n (%)	1,337 (53.5)	1,315 (52.9)	0.63
Female, n (%)	1,160 (46.5)	1,173 (47.1)	
Apgar Score at 5 minutes, n	2493	2485	
Apgar Score, mean (SD)	9.2 (1.0)	9.2 (1.0)	0.52
Apgar Score, Median (range)	9.0 (0–10)	9.0 (0–10)	0.99
Apgar Score < 4, n (%)	12 (0.48)	14 (0.56)	0.69

Table 2**Maternal and Infant Side Effects by Treatment Group**

	Chlorhexidine n (%)	Saline placebo n (%)	P-value
Maternal side effects at 30 minutes post-delivery	2,503	2,498	
Itching	8 (0.3)	1 (0.0)	0.04
Burning	11 (0.4)	3 (0.1)	0.06
Tenderness	0 (0.0)	0 (0.0)	--
Swelling	1 (0.0)	0 (0.0)	1.00
Infant side effects 30 minutes after wash	2,478	2,468	
Rash	1 (0.0)	5 (0.2)	0.12
Redness	1 (0.0)	7 (0.3)	0.04
Tenderness	0 (0.0)	0 (0.0)	--
Swelling	0 (0.0)	1 (0.0)	0.50

Table 3

Neonatal Outcomes by Treatment Group

	Chlorhexidine n (%)	Saline placebo n (%)	RR (95% CI)	P-value
<i>7-Day Outcomes</i>				
7-day/neonatal mortality or neonatal sepsis	77 (3.1)	84 (3.4)	0.91 (0.67, 1.24)	0.57
7-day/neonatal mortality	46 (1.9)	49 (2.0)	0.94 (0.63, 1.40)	0.75
7-day neonatal sepsis	31 (1.3)	35 (1.4)	0.88 (0.55, 1.43)	0.61
<i>28-Day Outcomes</i>				
28-day/neonatal mortality or neonatal sepsis	93 (3.8)	96 (3.9)	0.96 (0.73, 1.27)	0.79
28-day/neonatal mortality	55 (2.2)	56 (2.3)	0.98 (0.68, 1.41)	0.90
28-day neonatal sepsis	38 (1.6)	40 (1.7)	0.94 (0.61, 1.47)	0.80
<i>Other Outcomes</i>				
Infant in hospital at day 7 follow-up	43 (1.7)	48 (1.9)	0.89 (0.60, 1.35)	0.59
Infant hospitalized post discharge 28 days	51 (2.1)	50 (2.0)	1.02 (0.69, 1.50)	0.93

Table 4

Skin Infection by Treatment Group

	Day 7		Day 14 ^a		Day 28	
	Chlorhexidine n (%)	Saline placebo n (%)	Chlorhexidine n (%)	Saline placebo n (%)	Chlorhexidine n (%)	Saline placebo n (%)
Any Skin infection	82 (3.3)	203 (8.2) ^b	61 (8.6)	62 (8.9)	45 (1.8)	46 (1.9)
Type of infection						
Bulbous	8 (0.3)	24 (1.0) ^c	5 (0.7)	12 (1.7)	11 (0.4)	9 (0.4)
Pustular	72 (2.9)	184 (7.4) ^b	50 (7.0)	45 (6.4)	27 (1.1)	26 (1.1)
Vesicular	6 (0.2)	5 (0.2)	3 (0.4)	1 (0.1)	1 (0.0)	3 (0.1)
Cellulitis	0 (0.0)	5 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)

^aDay 14 included a subset of 1,412 subjects.^bp<0.0001^cp<0.005

Table 5

Maternal Secondary Outcomes by Treatment Group

	Chlorhexidine n (%)	Saline placebo n (%)	RR (95% CI)	P-value
Maternal death ^a	1 (0.0)	2 (0.1)	0.50 (0.01, 9.60)	0.62
Foul smelling vaginal discharge day 7	10 (0.4)	13 (0.5)	0.77 (0.34, 1.75)	0.53
Purulent vaginal discharge day 7 ^a	5 (0.2)	3 (0.1)	1.66 (0.32, 10.73)	0.73
Tender uterus day 7	7 (0.3)	6 (0.2)	1.16 (0.39, 3.46)	0.78
Mother in hospital at day 7 follow-up	14 (0.6)	28 (1.1)	0.50 (0.26, 0.94)	0.03
Foul smelling vaginal discharge day 28	13 (0.5)	13 (0.5)	1.00 (0.46, 2.14)	0.99
Mother in hospital at day 28 follow-up ^a	2 (0.1)	1 (0.0)	1.99 (0.10, 117.38)	1.00

^a Due to sparse data exact odds ratios were calculated instead of relative risks.