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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

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Summary

Background **Umbilical cord infection (omphalitis) is a risk factor for neonatal sepsis and mortality in low-resource settings where home deliveries are common. We aimed to assess the effect of umbilical-cord cleansing with 4% chlorhexidine (CHX) solution, with or without handwashing with antiseptic soap, on the incidence of omphalitis and neonatal mortality.**

Methods **We did a two-by-two factorial, cluster-randomised trial in Dadu, a rural area of Sindh province, Pakistan. Clusters were defined as the population covered by a functional traditional birth attendant (TBA), and were randomly allocated to one of four groups (groups A to D) with a computer-generated random number sequence. Implementation and data collection teams were masked to allocation. Liveborn infants delivered by participating TBAs who received birth kits were eligible for enrolment in the study. One intervention comprised birth kits containing 4% CHX solution for application to the cord at birth by TBAs and once daily by family members for up to 14 days along with soap and educational messages promoting handwashing. One intervention was CHX solution only and another was handwashing only. Standard dry cord care was promoted in the control group. The primary outcomes were incidence of neonatal omphalitis and neonatal mortality. The trial is registered with ClinicalTrials.gov, number NCT00682006.**

Findings **187 clusters were randomly allocated to one of the four study groups. Of 9741 newborn babies delivered by participating TBAs, factorial analysis indicated a reduction in risk of omphalitis with CHX application (risk ratio [RR]=0·58, 95% CI 0·41–0·82; p=0·002) but no evidence of an effect of handwashing (RR=0·83, 0·61–1·13; p=0·24). We recorded strong evidence of a reduction in neonatal mortality in neonates who received CHX cleansing (RR=0·62, 95 % CI 0·45–0·85; p=0·003) but no evidence of an effect of handwashing promotion on neonatal mortality (RR=1·08, 0·79–1·48; p=0·62). We recorded no serious adverse events.**

Interpretation **Application of 4% CHX to the umbilical cord was effective in reducing the risk of omphalitis and neonatal mortality in rural Pakistan. Provision of CHX in birth kits might be a useful strategy for the prevention of neonatal mortality in high-mortality settings.**

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Introduction

Of the 3·3 million annual neonatal deaths that occur worldwide, more than 99% occur in low-income and middle-income countries and about a third are attributed to infections.[1] Infection risk is greatest in countries where most deliveries (>70%) take place at home, often attended by unskilled traditional birth attendants (TBAs) with suboptimal conditions and delivery practices.[2,3] Compounding these problems are high rates of low birthweight and preterm birth, often associated with increased risk of infections.[4]

Pakistan has one of the highest neonatal mortality rates in the world (53 deaths per 10 000 livebirths) and up to 30% of neonatal deaths in Pakistan are attributed to sepsis.[5] Unsafe practices such as cutting the umbilical cord with unsterilised instruments and application of substances such as ash, lead-based concoctions (known locally as surma), oil, and, rarely, cow dung are practised in many rural areas of Pakistan[6] and associated with high risk of neonatal sepsis and mortality.[7] A range of available approaches have the potential to reduce the risk of neonatal infections. These include hygiene promotion (including handwashing), skin cleansing with antiseptics such as chlorhexidine (CHX), and promotion and use of clean birth kits. However, other than handwashing, provision of clean birth kits, and early initiation of breastfeeding, no other intervention to prevent neonatal infections is recommended for large scale implementation.[8–11]

Cord care is an important component of immediate neonatal care. On the basis of the findings of a Cochrane review by Zupan and colleagues,[12] WHO recommends dry care of the neonatal umbilical cord. The Cochrane review included 22 trials with a total of 8959 babies and examined various types of antiseptics applied to the umbilical cord. All the included studies were done in

hospital settings and, with the exception of one trial from Thailand,[13] in high-income countries. No systemic infections or deaths were reported in any of the trials and no differences in risk of umbilical cord infection were identified when the use of a topical antiseptic was compared with dry cord care or placebo, resulting in the recommendation of dry cord care. However, the validity of this recommendation for community settings in low-income countries, where the prevalence and risks of cord infection are much higher,[3] is questionable.

A community-based effectiveness trial of the application of CHX to the umbilical cord in Nepal[14] reported promising results with 75% reduction in the incidence of severe omphalitis and 24% reduction in neonatal mortality in infants who received topical CHX as opposed to dry cord care. Handwashing with soap has also shown promising results in community settings.[15,16] A cohort study from Nepal reported reduced risks of neonatal mortality associated with birth-attendant handwashing (relative risk [RR]=0·81, 95% CI 0·66–0·99), maternal handwashing (RR=0·56, 0·38–0·82), and when handwashing was practised by both the mother and birth attendant (RR=0·59, 0·37–0·94).[8]

Neither of these studies were done in health systems that used feasible and cost-effective delivery strategies and existing resources. We therefore designed an effectiveness trial to assess the feasibility of cleansing the umbilical cord with 4% CHX solution with or without handwashing with antiseptic soap, and to assess the effect of promotion of these interventions through TBAs on the incidence of omphalitis and neonatal mortality.

See Online for webappendix

Methods

Study area and population

We did a cluster-randomised trial in Dadu, a resource-poor rural district in Sindh province, Pakistan, with a population of about 1 million people and an infant mortality rate of 90 per 1000 livebirths.[17] Most (>80%) deliveries in the district are done at home by TBAs. The study interventions were delivered at the household level by TBAs working under the supervision of locally recruited community health workers (CHWs). All newborn babies delivered participating TBAs were eligible for enrolment in the study. Babies delivered in facilities or at home by care providers who were not part of this study were excluded, as were babies with obvious congenital or birth defects or cord anomalies noted at birth.

The study was approved by the Ethics Review Committee for Research of the Aga Khan University (Karachi, Pakistan). The project was overseen by an independent data safety and monitoring board, which ratified the design, met twice to assess the data, and recommended completion of the study as per protocol in its final meeting in April, 2009. The trial is registered with ClinicalTrials.gov, number NCT00682006.

Randomisation and masking

With a two-by-two factorial design, the clusters were randomly allocated to one of four groups (groups A to D) with a computer-generated random sequence. The random allocation sequence was generated independently by a statistician, who had no further involvement with the project. The code was available only to the pharmacy that prepared the CHX solution and included it in the birth kits. The birth kits were numbered and coded but otherwise identical. Implementation and data collection teams were masked to allocation.

Study design and procedures

The study area was divided into clusters defined on the basis of the population covered by a functional TBA (one who attended at least two deliveries per month). Clusters were typically one or two villages with a population of about 1000 people and care was taken to avoid villages with overlapping TBAs. TBAs provided families in group A with a clean birth kit, which included 4% CHX solution and a bar of soap (Life Buoy, Unilever Pakistan Ltd; containing phenol and carbolic acid). The 4% CHX solution was prepared in the Aga Khan University Pharmacy services by diluting 20% chlorhexidine digluconate (Sigma Aldrich, St Louis, MO, USA) in distilled water. It was provided in a 30 mL plastic bottle with sufficient CHX for up to 14 applications. The first application of CHX to the cord was done by the TBA after tying the cord with the clean tie provided in the birth kit. The TBA moistened a cotton ball with CHX solution and gently dabbed the solution on the umbilical cord stump. A second CHX-soaked cotton ball was used to gently cleanse the base of the stump and the skin immediately around the base (see webappendix for further details). The TBA demonstrated this method of CHX application to mothers and other caregivers after the delivery of newborn babies at the time of the first application and gave the CHX bottle to the family. Caregivers were advised to apply the CHX solution once a day for 14 days after birth, irrespective of the status of the umbilical cord. Family members were also encouraged by the TBA to wash their hands with soap and water before handling the newborn infant.

Families in group B were provided with a birth kit containing a bar of soap but no CHX, and received the same messages as did families in group A concerning handwashing with soap and water. They were advised to practise standard dry cord care. Families in group C received birth kits with 4% CHX solution but no bar of soap. As in group A, the TBA did the first application of CHX to the cord stump and instructed family members on subsequent applications. No handwashing promotion was undertaken in this group by TBAs. Families in group D (control cluster) received standard birth kits (without any CHX solution or soap). They were advised to practise dry cord care. No handwashing promotion was undertaken in this group by TBAs.

Panel: Research in context

Systematic review

We searched PubMed and the Cochrane Library with no date restrictions, using a combination of the search terms "chlorhexidine", "umbilical cord", and "omphalitis", and also screened the references of relevant articles manually. Our search of PubMed identified 209 studies, including a community randomised controlled trial from Nepal[8] and a study protocol for an ongoing randomised trial in Bangladesh.[18] We also identified a review of the safety aspects of chlorhexidine use in newborn infants, which did not suggest any major safety issues.[19]

Interpretation

The total number of children studied in the Nepal trial[14] was 15 123 (413 clusters). Application of chlorhexidine reduced the frequency of omphalitis by 32% to 75%, depending on the definition of omphalitis. Neonatal mortality was 24% lower in the chlorhexidine group (RR 0·76, 95% CI 0·55–1·04) than it was in the dry cord care group. Our study shows similar effect sizes to those recorded in the Nepal trial. If we pool our mortality results with those of the Nepal trial, the combined results show a reduction of 31% (RR 0·69, 0·55–0·86) in neonatal mortality. These results of two trials done in community settings lend support to the policy of application of chlorhexidine on newborn umbilical cord for prevention of omphalitis and mortality.

Before the study started, TBAs in the respective intervention groups underwent a 3 day training programme, as appropriate, on promotion of handwashing with soap and water, method of application of 4% CHX solution to the cord stump, and safe delivery practices. TBAs in control clusters were trained in safe delivery practices and standard immediate neonatal care, including promotion of dry cord care. When a TBA identified a pregnancy in the study area, she informed the CHW who then provided her with an appropriate birth kit for delivery to the family near term.

Data collection

Before the start of the intervention (October–December, 2007), we did a household survey of the study area to collect demographic information, and data for care-seeking practices, infant and neonatal mortality data, and birth and neonatal care practices, with a special focus on cord care. A team of trained CHWs (213 in total, one or two CHWs per cluster) collected information about neonatal outcomes through regular home visits with standardised data collection forms. The CHWs had a minimum of grade eight education, and were selected from the villages in which they were to work. They received 5 days of training in the recognition and grading of omphalitis with the help of audiovisual aids and pictorials and in recognition of neonatal danger signs from faculty members of the Department of Pediatrics, Aga Khan University. 12 training workshops were held for TBAs and

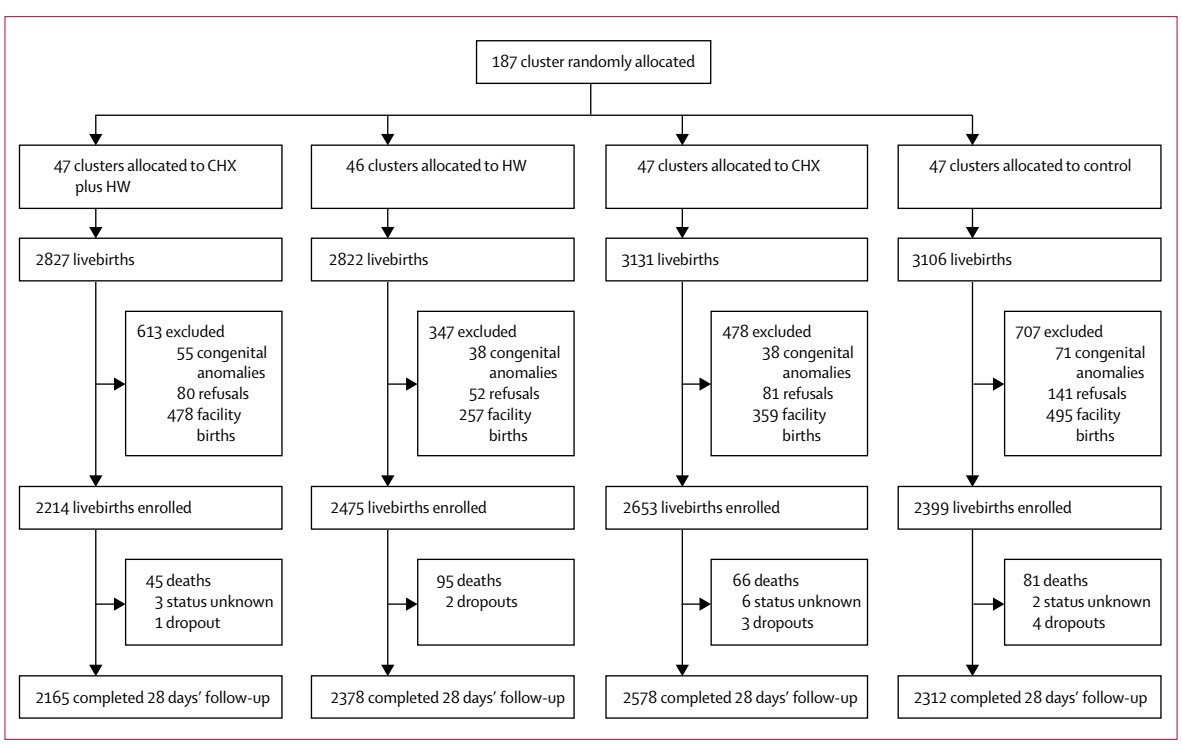

Figure 1: **Trial profile**
CHX=chlorhexidine cleansing. HW=handwashing.

	Chlorhexidine and handwashing (group A)	Handwashing only (group B)	Chlorhexidine only (group C)	Control (group D)
Households completing baseline survey	7866 (99%)	7736 (99%)	8457 (99 %)	8466 (99%)
Subdistrict				
Mehar	3565 (45%)	2526 (33%)	4167 (49%)	4519 (53%)
K N Shah	911 (12%)	1182 (15%)	936 (11%)	1266 (15%)
Dadu	1710 (22%)	1991 (26%)	1908 (23%)	1379 (16%)
Johi	1680 (21%)	2037 (26%)	1446 (17%)	1302 (15%)
Monthly household income				
≤5000 PKR	4924 (63%)	4866 (63%)	5138 (61%)	5708 (68%)
>5000 PKR	2162 (28%)	2141 (28%)	2626 (31%)	2297 (27%)
Not reported	767 (10%)	719 (9%)	678 (8%)	441 (5%)
Households owning own home	7769 (99%)	7624 (99%)	8367 (990%)	8346 (99%)
Main cooking fuel				
Animal dung	3776 (48%)	3369 (44%)	3415 (41%)	4158 (49%)
Firewood	3152 (40%)	3571 (46%)	3677 (44%)	3109 (37%)
Gas	706 (9%)	617 (8%)	1086 (13%)	1000 (12%)
Other	229 (2%)	173 (2%)	274 (3%)	190 (2%)
Main drinking water source				
Private tap	454 (6%)	673 (9%)	656 (8%)	537 (6%)
Private pump	5559 (71%)	5275 (68%)	5722 (68%)	5408 (64%)
Other	1845 (24%)	1783 (23%)	2073 (25%)	2511 (30%)
Sanitation				
None	3258 (42%)	3511 (45%)	3984 (47%)	4079 (48%)
Pit latrine	2624 (33%)	2307 (30%)	2721 (32%)	2560 (30%)
Flush toilet	1953 (25%)	1888 (24%)	1709 (20%)	1797 (23%)
Married women aged 15–49 years	9424	9405	10 438	10 353
Median age (IQR) in years	30 (25–35)	30 (25–35)	30 (25–35)	30 (25–35)
Maternal literacy	878 (9%)	969 (10%)	1257 (12%)	970 (9%)
Handwashing after defecation				
Do not wash	140 (2%)	84 (1%)	150 (2%)	117 (1%)
Washed with water only	2358 (30%)	1751 (23%)	2046 (25%)	2116 (25%)
Washed with soap and water	5206 (67%)	5724 (75%)	6071 (73%)	6048 (73%)
Handwashing before handling newborn baby				
Never	558 (7%)	654 (9%)	616 (7%)	674 (8%)
Sometimes	3411 (44%)	2837 (37%)	3652 (44%)	3488 (42%)
Always	3783 (49%)	4115 (54%)	4051 (49%)	4163 (50%)
Number of pregnant women	1352 (15%)	1377 (15%)	1574 (15%)	1608 (16%)
Number of pregnant women attending antenatal care				
Yes	454 (34%)	436 (32%)	617 (39%)	591 (37%)
No	797 (59%)	841 (61%)	825 (52%)	923 (57%)
Not recorded	101 (8%)	100 (7%)	132 (8%)	94 (6%)
Number of women who delivered during the past year	2320	2510	2668	2404
Outcome of most recent pregnancy				
Miscarriage	151 (7%)	246 (10%)	301 (11%)	190 (8%)
Stillbirth	137 (6%)	218 (9%)	248 (9%)	120 (5%)
Livebirth	2032 (88%)	2046 (82%)	2118 (79%)	2094 (87%)
Place of most recent delivery				
Home	1690 (73%)	1854 (74%)	1944 (73%)	1971 (82%)

(Continues on next page)

9 training workshops were held for CHWs, with 20–25 participants per session. The CHWs maintained close contact with TBAs, were informed of all pregnancies, and provided TBAs with birth kits as needed. Each CHW was provided with a stock of only one type of birth kit, appropriate to the cluster allocation. They visited all newborn babies on prespecified days (days 1, 3, 5, 7, 14, and 28) to assess the newborn baby for visible signs of cord infection (omphalitis) and general wellbeing with standardised assessment forms. The day 1 assessment form focused on delivery and immediate neonatal care practices (eg, source and use of clean delivery kit, bathing and massage practices, cord applications after birth, and breastfeeding) as well as TBA handwashing practices reported by the family. Assessments on days 3, 5, 7, and 14 focused on presence of omphalitis, other neonatal morbidities and reported CHX application for groups A and C. The day 14 and day 28 assessments also recorded neonatal illnesses since day 7, care seeking, and mortality.

If the CHWs detected a newborn baby with moderate to severe omphalitis, the baby was immediately referred to the nearest government health facility for further assessment and management. In the event that such referral was not possible or was not accepted by the family, the family were asked to seek care from the closest private practitioner. No home-based treatment was provided. Two senior medical officers employed by the project were responsible for supervision of field staff to ensure data quality, and liaison with the communities and other stakeholders, including district health administration.

The primary outcomes of the trial were incidence of neonatal omphalitis and neonatal mortality. Omphalitis was defined as the presence of signs of inflammation such as redness and swelling (oedema) or pus of either the cord stump or the skin at the base of stump and graded into four categories: no omphalitis (no redness, swelling, or pus), mild omphalitis (redness, swelling, or pus restricted to the cord stump), moderate omphalitis (redness, swelling, or pus extending to the skin at the base of the cord stump less than 2 cm), or severe omphalitis (inflammation extending more than 2 cm from the cord stump, with or without pus).

We did a systematic review of safety of CHX before the study began (panel), which did not suggest any substantial adverse effects other than a slight delay in cord separation with CHX use. Additional information on the safety of chlorhexidine applications to the newborn babies was also available from a local study in newborn infants delivered in facility settings,[20] which did not record any serious problems. Nevertheless, CHWs were asked to report any problems, including neonatal seizures, local skin burns, or delay in separation of the cord.

Statistical analysis

Information about village populations, location in reference to health facilities, numbers of TBAs, and presence of other CHWs (private sector or public sector

by so-called Lady Health Workers [LHWs]) was obtained through a baseline census. Neonatal mortality was estimated by recall of livebirths in the preceding 12 months and compared between clusters. Suitable clusters with defined TBAs and population characteristics were independently matched and allocated to one of four intervention groups.

No reliable information exists for the population-level risk of neonatal omphalitis in Pakistan, hence a baseline omphalitis rate of 190 per 1000 livebirths was assumed on the basis of the results of the baseline survey. The trial was designed to detect a 35% reduction in incidence of cord infection, irrespective of the intervention used, with 90% power, and 5% two-sided type 1 error, assuming an intracluster correlation coefficient of 0·08 and assuming no interaction between handwashing and CHX. With an expected birth rate of 30 per 1000 population and a planned period of recruitment of 12 months, we estimated a required sample of 208 clusters (52 clusters per group with about 1500 births per annum per group.[21] However, of a possible 220 clusters in the area, 33 clusters (44 villages) were considered too dangerous for field operations, so only 187 clusters were available and randomly allocated to the four study groups.

Omphalitis was defined for every child as one or more cord assessment meeting the study criteria for infection. We did binomial regression, to provide risk ratio estimates, on individual-level data with generalised estimating equations with robust SEs to account for the cluster randomisation.[22] In view of the factorial design, we did both marginal and between-group analyses. We did Wald tests to assess the evidence of interaction between the interventions. We used SPSS (version 16) and Stata (version 11) for all analysis.

Role of the funding source

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

Results

Between January, 2008, and June, 2009, 11886 livebirths were reported from the study area, of which 2145 were excluded; we enrolled 9741 babies into the trial (figure 1). Baseline socioeconomic, household, and maternal characteristics were much the same between the four groups (table 1). Almost 90% of households (7213 of 8290) practiced application of traditional substances (oil, surma, coal) on the cord.

Most (2118 [97%]) care providers of enrolled infants in groups A and C reported at least one CHX application and 1330 (63%) of mothers in these groups reported application of CHX at least three times a day. The overall mean duration of CHX application in these two groups was 11·1 days (SD 2·8) with a mean 2·4 (SD 0·7) applications per day. We recorded no difference in the time to separation of the cord between groups (group A, mean 6·2 days [SD 1·3]; group B, 5·9 days [1·5]; groups C and D, both 6·0 days [1·6]). Almost all families (2168 [99%]) in groups A and B confirmed receipt of a bar of soap in the birth kits provided and reported handwashing on average three times a day. 1850 (85%) mothers reported continuation of handwashing for more than 10 days in both handwashing promotion groups (groups A and B).

	Chlorhexidine and handwashing (group A)	Handwashing only (group B)	Chlorhexidine only (group C)	Control (group D)
(Continued from previous page)				
Hospital	524 (23%)	620 (25%)	708 (27%)	427 (18%)
Delivery attendant during most recent delivery				
Unskilled (traditional birth attendant, Dai, or family member)	1772 (76%)	1880 (75%)	1953 (73%)	1971 (82%)
Skilled (doctor or lady health visitor)	548 (24%)	630 (25%)	715 (27%)	433 (18%)
Use of clean delivery kit during last delivery				
Yes	469 (23%)	411 (20%)	608 (29%)	574 (27%)
No	1368 (67%)	1498 (73%)	1292 (61%)	1326 (63%)
Unknown	195 (10%)	137 (7%)	216 (10%)	193 (9%)
Home application to cord				
Home application	1766 (87%)	1852 (91%)	1692 (80%)	1903 (91%)
Home antiseptic	266 (13%)	194 (10%)	426 (20%)	191 (9%)
Breastfeeding initiation time				
Within 1 h of birth	1441 (71%)	1555 (76%)	1483 (70%)	1527 (73%)
1–3 h after birth	410 (20%)	344 (17%)	457 (22%)	387 (19%)
More than 3 h after birth	181 (9%)	147 (7%)	178 (8%)	180 (9%)

PKR=Pakistani Rupees.

Table 1: **Baseline household characteristics**

	Number of livebirths	Number of omphalitis cases	Risk ratio (95% CI)	p value
Treatment group analysis				0·0004
Handwashing plus chlorhexidine cleansing (group A)	2214	82	0·53 (0·32–0·88)	
Handwashing only (group B)	2475	127	0·67 (0·48–0·93)	
Chlorhexidine cleansing only (group C)	2653	84	0·44 (0·29–0·67)	
Control (group D)	2399	182	1·0	
Factorial analysis (handwashing *vs* no handwashing)				0·24
No handwashing (groups C and D)	5052	266	1·0	
Handwashing (groups A and B)	4689	209	0·83 (0·61–1·13)	
Factorial analysis (chlorhexidine cleansing *vs* no chlorhexidine cleansing)				0·002
No chlorhexidine cleansing (groups B and D)	4874	309	1·0	
Chlorhexidine cleansing (groups A and C)	4867	166	0·58 (0·41–0·82)	
Total	9741	475		

Table 2: **Incidence of omphalitis**

	Number of livebirths	Number of neonatal deaths	Neonatal mortality rate (per 1000 livebirths)	Risk ratio (95% CI)	p value
Treatment group analysis					0·03
Handwashing plus Chlorhexidine cleansing (group A)	2214	45	20·3	0·64 (0·39–1·06)	
Handwashing only (group B)	2475	95	38·4	1·23 (0·82–1·83)	
Chlorhexidine cleansing only (group C)	2653	66	24·9	0·74 (0·50–1·08)	
Control (D)	2399	81	33·8	1·0	
Factorial analysis (handwashing *vs* no handwashing)					0·62
No handwashing (groups C and D)	5052	147	29·1	1·0*	
Handwashing (groups A and B)	4689	140	29·9	1·08 (0·79–1·48)*	
Factorial analysis (chlorhexidine cleansing *vs* no chlorhexidine cleansing)					0·003
No chlorhexidine cleansing (groups B and D)	4874	176	36·1	1·0*	
Chlorhexidine cleansing (groups A and C)	4867	111	22·8	0·62 (0·45–0·85)*	
Total	9741	287	29·5		

*No evidence of interaction between the two groups (p=0·3).

Table 3: **All-cause neonatal mortality**

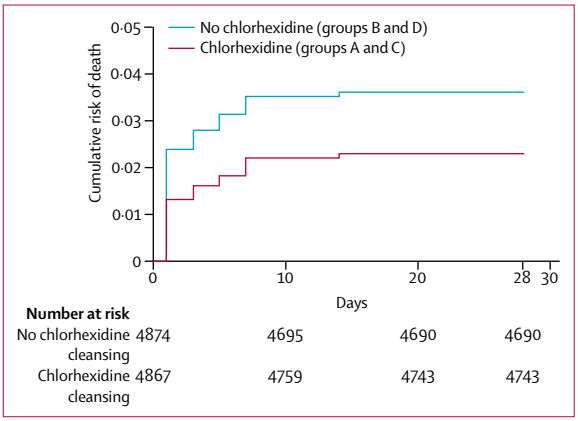

Figure 2: **Cumulative risk of neonatal mortality**

The risk of omphalitis (any grade) was lower in all three treatment groups than it was in the control group (table 2). We did not record a statistically significant interaction between CHX and handwashing (p=0·09). A factorial analysis, including CHX and handwashing as main effects only, indicated strong evidence of a reduction in risk of omphalitis associated with CHX application but provided no evidence of an independent effect of handwashing (table 2). This analysis was done on the basis of the broadest definition of omphalitis (ie, pus or mild, moderate, or severe redness, or mild, moderate, or severe swelling). An analysis done on the basis of severity of infection showed that risk of omphalitis was reduced across all categories of infection with no clear gradient (webappendix).

The overall neonatal mortality rate was 29·4 per 1000 livebirths, with evidence of variation between the three treatment groups (table 3). We recoded no evidence of an interaction between CHX application and handwashing (table 3). A factorial analysis, including CHX and handwashing as main effects only, indicated strong evidence of a reduction in neonatal mortality in children receiving CHX but no evidence that handwashing promotion was associated with a reduction in neonatal mortality (table 3 and figure 2). Additional factorial analysis at 6 months' follow-up for infants aged 1–6 months showed no evidence that handwashing was associated with any reduction in infant mortality (RR 0·79, 95% CI 0·45–1·41; webappendix).

Discussion

Our findings shows that the application of CHX to the umbilical cord of a newborn baby can reduce the incidence of neonatal omphalitis and neonatal mortality compared with the recommendation to families of dry cord care or handwashing only. The umbilical cord of a newborn baby is easily colonised by microorganisms and bacteria.[23] The rate of bacterial colonisation in the early neonatal period is closely related with the incidence of neonatal sepsis,[24–26] suggesting the need for early intervention. The widespread application of harmful substances to the cord stump, seen in many resource-poor urban and rural settings, can aid the entrance of microorganisms and skin flora into the blood stream, leading to infection and omphalitis.[3]

Our trial was designed to assess the acceptability and effectiveness of CHX with a delivery strategy that could be emulated by the public sector, using existing health-care workers, including TBAs. TBAs attend a large proportion of deliveries at household level but their work is likely to be phased out by community midwives in due course. We deliberately chose to train and deploy CHWs to link with TBAs, because the training and deployment of such CHWs is already part of a national policy in Pakistan.[27] However, the existing cadre of LHWs do not work closely with TBAs, nor are birth kits part of the set of interventions available to them. Our finding that risk of omphalitis was lower (by as much as 42% on factorial analysis) when a baby's umbilical cord was cleaned with CHX by TBAs and family members at home compared with when CHX was not used, and the 38% reduction in neonatal mortality in the groups receiving CHX compared with those not receiving CHX, is of public health importance and could be emulated by any type of health worker engaged in domiciliary births. These findings are similar to those seen in rural southern Nepal by Mullany and colleagues,[14] who reported a 32–75% reduction in the incidence of omphalitis and a 24% reduction in neonatal mortality in infants receiving cord cleansing with CHX compared with those receiving dry cord care. In Nepal,

the protective effect of the intervention was most apparent when the application of CHX was made in the first 24 h of birth and no difference between the groups was seen when cord cleansing was initiated after 24 h.

We did not record any protective effect of handwashing promotion on the incidence of omphalitis and neonatal mortality in factorial analyses. Possible explanations for this could be that reported handwashing was not the same as actual handwashing practices, or that despite handwashing, the practice of application of different materials on neonatal umbilical cords continued in the community. In the latter scenario, promotion of handwashing alone might not be enough to reduce the incidence of omphalitis. Our data suggest that families continued to apply other traditional materials to the cord at birth and that these practices were similar in all four groups (data not shown). The most widely used substance was surma, which is a traditional cosmetic for eyes. Surma is composed of ground lead, which not only causes a local reaction but can also lead to systemic lead toxicity.[28–30] The local reaction can provide substrate for invasion of microorganisms, which can lead to local and systemic infection.

Cleansing of the umbilical cord with CHX is regarded as safe.[31] CHX is a broad-spectrum antiseptic extensively used in dental, obstetric, and surgical cleaning products. It has also been used in obstetrics, peripartum, perineal, and vaginal washes in concentrations as high as 4%.[32] Safety studies in newborn infants exposed to CHX washes in various concentrations showed no evidence of toxic effects, even in babies in whom transcutaneous absorption could have occurred. CHX is included in WHO's essential drugs list,[33] and is the antiseptic of choice for cord care in hospital. Although we promoted a once daily application, most families used it more frequently, which is an additional indicator of acceptability. We did not record any excess in reported neonatal morbidities such as seizures or skin burns in the groups receiving CHX.

Our study had several limitations. We had fewer clusters than estimated initially because of problems with access and security in some villages, reducing the power of the study to detect any effect of handwashing. Another limitation is that although the CHWs were able to undertake almost all the planned postnatal visits, they were unable to attend all births and hence did not witness initial application and family instruction directly. Although we believe that their capture of information pertaining to all livebirths is reliable, they could have missed some very early neonatal deaths. Despite the training and supervision, the ability of the CHWs to diagnose and detect various grades of omphalitis can be questioned. Medical officers could not feasibly have done all postnatal examinations in a timely manner, and this limitation could have introduced other biases. The information about family practices is based on reported practices rather than direct observations. We do not believe that these issues affected our findings because the total number of livebirths reported in all clusters was much the same. Although CHWs were aware of the type of birth kit in their cluster, they were not told explicitly what the primary outcomes of interest were. We took care in the original definition of clusters to minimise the risk of contamination. We do not believe that any overlap occurred between groups during the study because no movement of TBAs or CHWs between clusters was reported, nor was there any instance of misallocation of birth kits to target households. We do not have microbiological data because we could not culture the umbilical cord stump of infants to assess bacterial colonisation. However, we do not believe that any of these factors substantially invalidate our findings. We recorded very little loss to follow-up. Although the study was not powered to detect an interaction between handwashing and CHX, we recorded no synergistic effect when CHX was combined with handwashing promotion.

Our study provides strong evidence that in a water-scarce rural area of Pakistan with high neonatal mortality, provision of 4% CHX in birth kits, with application to the cord by TBAs and continued afterwards by family members, is effective in reducing the risk of omphalitis and neonatal mortality. By contrast with other trials,[34–36] we recorded no evidence to suggest that promotion of handwashing and provision of a medicated soap in birth kits had any effect on neonatal or infant mortality. We also did not find any evidence that the addition of handwashing promotion to CHX adds any benefit to that provided by CHX alone—caution should be exercised in the interpretation of this finding because we have only family-reported information about handwashing practices, rather than information about actual practices. The absence of a benefit of handwashing promotion and soap provision could be because of a failure of the promotional strategy rather than a failure of the practice of handwashing with soap.

We believe that these findings have substantial implications for public health in south Asia, where many areas share similar cultural, social, and economic characteristics. We adopted a feasible and low-cost approach to provision of 4% CHX in birth kits and recorded high rates of acceptability and use. Suxh provision of CHX with birth kits could be used as a rapid delivery strategy for scaling up intervention coverage at birth in both community settings and deliveries in public sector facilities. Further studies should assess the effectiveness of this approach in large scale programmes and we propose that this intervention be considered for possible inclusion in the range of interventions available to LHWs of the National Program for Family Planning and Primary Care of the Government of Pakistan.[37,38]

Contributors

ZAB had the idea for the study and, as principal investigator, was involved in all aspects of this study. SS, SC, AI, NA were involved in study design, analysis planning, interpretation of data, and writing of the paper. NB implemented the study at the field site. All authors reviewed and approved the final paper.

Conflicts of interest
All authors declare that they have no conflicts of interest.

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References

1 Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; **365:** 891–900.
2 Darmstadt GL, Lee AC, Cousens S, et al. 60 million non-facility births: who can deliver in community settings to reduce intrapartum-related deaths? *Int J Gynaecol Obstet* 2009; **107** (suppl 1): S89–112.
3 Mullany LC, Darmstadt GL, Katz J, et al. Risk factors for umbilical cord infection among newborns of southern Nepal. *Am J Epidemiol* 2007; **165:** 203–11.
4 Qadir A, Bhutta ZA. Low birthweight in developing countries. In: Kiess W, Chernausek SD, Hokken-Koelega ACS, eds. Small for gestational age causes and consequences. *Pediatr Adolesc Med*. Basel: Karger, 2009: 148–62.
5 National Institute of Population Studies (NIPS) [Pakistan], and Macro International Inc. 2008. Pakistan Demographic and Health Survey 2006–07. http://www.measuredhs.com/pubs/pdf/FR200/FR200.pdf (Jan 21, 2012).
6 Bhutta ZA, Ali N, Hyder A, Wajid A. Perinatal and newborn care in Pakistan: seeing the unseen. Karachi: Oxford University Press, 2004.
7 Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. *Pediatr Infect Dis J* 2009; **28** (suppl 1): S3–9.
8 Rhee V, Mullany LC, Khatry SK, et al. Maternal and birth attendant hand washing and neonatal mortality in southern Nepal. *Arch Pediatr Adolesc Med* 2008; **162:** 603–08.
9 Cairncross S, Bartram J, Cumming O, Brocklehurst C. Hygiene, sanitation, and water: what needs to be done? *PLoS Med* 2010; **7:** e1000365.
10 Hundley VA, Avan BI, Braunholtz D, Graham WJ. Are birth kits a good idea? A systematic review of the evidence. *Midwifery* 2011; published online May 9. DOI:10.1016/j.midw.2011.03.004.
11 Parashar UD, Bennett JV, Boring JR, Hlady WG. Topical antimicrobials applied to the umbilical cord stump: a new intervention against neonatal tetanus. *Int J Epidemiol* 1998; **27:** 904–08.
12 Zupan J, Garner P, Omari AA. Topical umbilical cord care at birth. *Cochrane Database Syst Rev* 2004; **3:** CD001057.
13 Panyavudhikrai S, Danchaivijitr S, Vantanasiri C, et al. Antiseptics for preventing omphalitis. *J Med Assoc Thai* 2002; **85:** 229–34.
14 Mullany 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.
15 Luby SP, Agboatwalla M, Feikin DR, et al. Effect of handwashing on child health: a randomised controlled trial. *Lancet* 2005; **366:** 225–33.
16 Cairncross S, Hunt C, Boisson S, et al. Water, sanitation and hygiene for the prevention of diarrhoea. *Int J Epidemiol* 2010; **39** (suppl 1): i193–205.
17 District health profile—Dadu 2005, Pakistan initiative for mothers and newborns (PAIMAN). http://paiman.jsi.com/Resources/Docs/district-health-profile-dadu.pdf (accessed Jan 26, 2011).
18 El Arifeen S, Mullany L, 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; published online Feb 8. DOI:10.1016/S0140-6736(11)61848-5.
19 Mullany LC, Darmstadt GL, Tielsch JM. Safety and impact of chlorhexidine antisepsis interventions for improving neonatal health in developing countries. *Pediatr Infect Dis J* 2006; **25:** 665–75.
20 Saleem S, Rouse DJ, McClure EM, et al. Chlorhexidine vaginal and infant wipes to reduce perinatal mortality and morbidity: a randomised controlled trial. *Obstet Gynecol* 2010; **115:** 1225–32.
21 Donner A, Klar N. Statistical considerations in the design and analysis of community intervention trials. *J Clin Epidemiol* 1996; **49:** 435–39.
22 Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; **73:** 13–22.
23 Mortimer EA Jr, Wolinsky E, Gonzaga AJ, Rammelkamp CH Jr. Role of airborne transmission in staphylococcal infections. *BMJ* 1966; **1:** 319–22.
24 Sarkany I, Gaylarde CC. Bacterial colonisation of the skin of the newborn. *J Pathol Bacteriol* 1968; **95:** 115–22.
25 Klein JO, Marcy SM. Infection in the newborn. *Clin Obstet Gynecol* 1970; **13:** 321–47.
26 Infection in the nursery. *BMJ* 1970; **3:** 235–36.
27 Hafeez A, Mohamud BK, Shiekh MR, Shah SA, Jooma R. Lady health workers programme in Pakistan: challenges, achievements and the way forward. *J Pak Med Assoc* 2011; **61:** 210–15.
28 al-Hazzaa SA, Krahn PM. Kohl: a hazardous eyeliner. *Int Ophthalmol* 1995; **19:** 83–88.
29 Patel AB, Belsare H, Banerjee A. Feeding practices and blood lead levels in infants in Nagpur, India. *Int J Occup Environ Health* 2011; **17:** 24–30.
30 Patel AB, Williams SV, Frumkin H, Kondawar VK, Glick H, Ganju AK. Blood lead in children and its determinants in Nagpur, India. *Int J Occup Environ Health* 2001; **7:** 119–26.
31 Denton GW. Chlorhexidine. In: Block SS, ed. Disinfection, sterilization, and preservation, 5th edn. Philadelphia: Lippencott Williams and Wilkens, 2001: 321–26.
32 McClure EM, Goldenberg RL, Brandes N, et al. The use of chlorhexidine to reduce maternal and neonatal mortality and morbidity in low-resource settings. *Int J Gynaecol Obstet* 2007; **97:** 89–94.
33 WHO. Essential medicines list 2011. http://www.who.int/selection_medicines/list/en/index.html (accessed Jan 21, 2012).
34 Kapoor SL, Reddaiah VP, Lobo J. Control of tetanus neonatorum in a rural area. *Indian J Pediatr* 1991; **58:** 341–344.
35 Meegan M, Conroy RM, Lengeny SO, Renhault K, Nyangole J. Effect on neonatal tetanus mortality after a culturally-based health promotion programme. *Lancet* 2001; **358:** 640–641.
36 Jokhio AH, Winter HR, Cheng KK. An intervention involving traditional birth attendants and perinatal and maternal mortality in Pakistan. *N Engl J Med* 2005; **352:** 2091–99.
37 Oxford Policy Management Group. Lady health worker programme: third party evaluation of performance. http://www.opml.co.uk/sites/opml/files/LHW_%20Management%20Review.pdf (accessed Jan 21, 2012).
38 Bhutta ZA, Soofi S, Cousens S, et al. Improvement of perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. *Lancet* 2011; **377:** 403–12.