Supplementary Appendix: 'Effect of an integrated neonatal care kit for improving neonatal health outcomes in a cluster-randomized controlled trial in rural Pakistan'

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Supplementary Methods

Study design and oversight

LHWs in the study clusters delivered both the intervention (integrated neonatal care kit (iNCK)) and control (standard of care) to study participants and did not receive financial compensation, beyond their regular government salary, for their role in this study. An allocation ratio of 1:1 was utilized to randomly assign clusters to a treatment group. Cluster-stratified randomization was performed by a scientist who was not directly involved in this research project. Since data collection visits could impact outcomes, the protocol included two phases, separated by 11-months, that differed in the timing and frequency of data collection visits. In phase two of the study, the number of data collection visits was reduced from five visits (days 1, 3, 7, 14 and 28) to two visits (days 8 and 28). Details pertaining to the first phase, which took place between April 2014 and August 2015, are reported here. While a formal survey of household-level baseline data was not collected in this work, baseline data were collected from over 67,000 households within 20 union councils in RYK as part of a study that was conducted 18 months before our trial (unpublished). These data were used to estimate baseline birth rates and newborn mortality rates (NMRs) in the study population. District health authorities in RYK including the District Health Office, LHW Program District Coordinator, and the Maternal Newborn Child Health (MNCH) Program District Coordinator were engaged prior to the study's launch and provided permission to conduct this effectiveness study through the local RYK health system infrastructure. The design and methods of the first phase of this trial were previously published[1]. All protocol amendments are summarized in Table S1.

Participants and procedures

Gestational age was estimated using self-reported first day of last menstrual period (LMP). Following delivery, data collectors, who had a minimum qualification of 14 years of schooling, were expected to visit participants' homes in both the intervention and control clusters on days 1 (or as soon as possible after delivery), 3, 7, 14, and 28. All newborns were weighed using a standardized hand-held scale provided by the study on the day that they were first visited by a data collector (day of newborn enrolment), and on days 7 and 28[1]. Weight measurements collected within the first 3 days of life by data collectors were used to assess the prevalence of low birth weight (LBW), which was defined as a weight of less than 2500 grams. All LBW babies identified by data collectors were referred to the nearest health facility. Participants self-reported whether their newborns were weighed by a LHW soon after delivery and the recalled weight that was measured by their LHW. In addition to LBW, data collectors were trained to identify and make referrals if they observed any of the following: omphalitis of any severity level (defined below), or severe infection that was defined in-part using the Integrated Management of Childhood Illness (IMCI) criteria as the presence of any one of the following symptoms: convulsions; tachypnea (60 breaths per minute or more); fever; severe chest indrawing; movement only when stimulated or no movement at all; reports that the newborn did not feed at all for at least 12 hours. With the exception of participant-reported feeding behaviors, all symptoms were directly observed or measured by a data collector.

Outcomes

Stillbirths were documented at the first study visit and were defined as newborns that did not breathe, cry, or move, at or any time after delivery. The severity of omphalitis was ascribed to one of three categories on the basis of inflammation that was directly observed by a data collector; if inflammation was limited to the umbilical stump, extended outwards from the base of the stump by less than 2 cm, or extended outwards from the base of the stump by more than 2 cm, then the omphalitis case was defined as mild, moderate, or severe, respectively. Severe infection, defined in-part using the Integrated Management of Childhood Illness (IMCI) criteria for a Possible Serious Bacterial Infection (PSBI), was stipulated as the presence of convulsions or fast breathing (60 breaths per minute or more) or fever or severe chest indrawing or movement only when stimulated or no movement at all or reports that the newborn did not feed at all for at least 12 hours[2]. Additional secondary outcomes, which will be reported elsewhere, included neurodevelopment measured at 12 months of age and the knowledge, attitude, practice, and willingness to pay for the iNCK. All outcome measures pertain to the individual and were adjusted for cluster allocation.

Gestational age was calculated using self-reported first day of last-menstrual period (LMP). Z-scores for weight for age (WAZ) and head circumference for age (HCAZ) at birth were calculated using the Intergrowth package [3]. WAZ values were flagged if they were less than -6 SD or greater than 5 SD from the median Intergrowth standards. HCAZ values were flagged if they were less than -5 SD or greater than 5 SD from the median Intergrowth standards. Biological plausibility was assessed on a case-by-case basis. Specifically, a pediatrician manually inspected all extreme values alongside gestational age and available weight and head circumference measurements, as well WAZ and HCAZ scores. Term LBW was defined as a newborn who was delivered at ≥37 weeks of gestation and was measured to weigh less than 2500 grams within their first 3 days of life. Newborns who had a WAZ at birth value less than -1.2816 were defined as small for gestational age.

Statistical methods

Between treatment-group comparisons were conducted using t-tests, chi-squared, Fisher's exact test, as appropriate for continuous or categorical variables. All tests of significance were two-sided and did not adjust for baseline covariates. Analyses for the study's primary outcome were performed independently by two different analysts.

In post-hoc, complete-case, ITT analyses we explored the effect of the intervention on outcomes stratified by place of delivery, timing of the newborn death (fewer than 7 completed days *vs.* after 7 but before 28 completed days), and timing and frequency of data-collector home visits, timing of iNCK and/or standard of care delivery, and gestational age of delivery were conducted. The denominator for late neonatal mortality rate was censored for early deaths. A post-hoc, complete-case, per protocol analysis of the effect of the intervention on neonatal mortality was also conducted. Compliance scores were calculated using self-reported data on the utilization of each iNCK component. Full compliance data were collected on days 3, 7, 14 and 28 of life among participants who were enrolled within the first 3 days of life. Participants were initially assigned a compliance score for each component of the iNCK that ranged from 0 to 3 (0=never used, 1=partial compliance, 2=good compliance, and 3=excellent compliance) (Table S2). The total compliance score for ThermoSpot took into account both utilization of the sticker and the participant's response to colour change (ThermalAction). In this manner, compliance scores were only assigned for the thermoregulatory components of the kit (i.e., reflective blanket and heat pack) if ThermoSpot was used and participants reported that the sticker changed colour to red or black (i.e., moderate or severe hypothermia, respectively). For example, if an individual received a score of 2 out of 3 based on their reported utilization of ThermoSpot and indicated that they sought health care after ThermoSpot turned blue (3/3), their combined total score of 5 was scaled to 2.5 out of 3. Compliance scores for individual iNCK components were summed and divided by the maximum possible iNCK compliance score (12 points). Participants with varying levels of compliance (i.e., 65%, 75%, 80%, 90%, 95%, and 100%) were compared to a 1:1 propensity-score matched subset in the control group in which propensity scores were based on maternal age, gravidity, total number of live children, delivery location, antenatal care, and the number of antenatal care visits (Table S8). Since compliance could not be measured in the standard of care group (i.e., a placebo was not possible), the effect of the intervention on mortality *within* the iNCK treatment group was also explored at varying levels of compliance (i.e., 65%, 75%, 80%, 90%, 95%, and 100%) (Table S9). In this manner, mortality among excellent compliers could be compared to mortality among non-excellent compliers.

In post-hoc, complete-case analyses the effect of the intervention on outcomes stratified by utilization of chlorhexidine (applied chlorhexidine on day 1 *vs.* applied chlorhexidine after day 1), and utilization of a clean delivery kit (did not use clean delivery kit in the intervention arm *vs.* did not use clean delivery kit in the standard of care arm and used clean delivery kit in the intervention arm *vs.* used clean delivery kit in the standard of care arm) were also explored.

Supplementary Tables

Table S1: Trial protocol amendments initiated after the first participant was enrolled

Item Number	Protocol Versions Date	Rationale for amendment
0	February 14, 2014	N/A: Date of initial protocol approved by the Research Ethics Board
1	April 29, 2014	• Added a new secondary outcome to the study (neurodevelopment at 12 months of age among a sub set of participants) • Built a birth cohort study into the control arm of the study
2	February 20, 2015	• Added a clear description of the methods used to collect verbal autopsies. The verbal autopsy form was approved in the initial submission in Feb. 2014. However, this amendment simply clarified the methods used for data collection (i.e., the grievance period etc.).
3	May 14, 2015	• Added a new secondary outcome to the study to assess the acceptability and willingness to pay for the kit among a sub-set of participants • Introduced a new brief questionnaire to collect pregnancy and neonatal outcomes from participants whose deliveries were not captured within the first 3 days of life
4	October 29, 2015	• Introduced the concept of a second phase to the study with a reduced data collection schedule (2 visits during the neonatal period instead of 5). The study's DSMB was consulted and approved the introduction of phase II. Importantly, at this stage, the phase II study was simply an idea and its implementation was pending funding.
5	January 29, 2016	• Revised sample size calculation for phase II study
6	August 8, 2016	• Funding was received for phase II of the study • Since at this point a large time gap existed between phases I and II of the study (11 months) we added a baseline data collection survey to better understand the landscape of RMNCH in the lag period between the two phases • Revised sample size calculation for phase II study (increased from 2400 to 3040 to account for 15% loss to follow-up and 10% to adjust for covariates between groups)
7	September 23, 2016	• Added information to the protocol to describe the methods for transferring data from Pakistan to SickKids via a secure online file transfer program
8	December 20, 2016	• Added approximately 2 sentences to the protocol to clarify that field workers observed LHW teaching and kept study logs as evidence that the kits were delivered

Table S2: Compliance score defined by individual iNCK component

	0	1	2	3
iNCK Component	**Never Used**	**Partial Compliance**	**Good Compliance**	**Excellent Compliance**
Clean Birth Kit (CBK)	Did not use the CBK **OR** Did not know if the CBK was used **AND** Delivery happened at home	Did not use the CBK **OR** Did not know if the CBK was used **AND** Delivery happened at "other" (i.e., TBA's house, LHV's house)	Did not use the CBK **OR** Did not know if the CBK was used **AND** Delivery happened at primary health care facility (i.e., BHU, RHC, private clinic, or Dispensary)	Used the CBK at the time of delivery; **OR** Did not use the CBK **OR** Did not know if the CBK was used **AND** delivery happened at hospital (THQ, DHQ, CMH, private hospital)
Chlorhexidine (CHX)	**Newborns that Survived Neonatal Period**: Never applied CHX to umbilical stump **Newborns that did NOT Survive Neonatal Period:** Never applied CHX to umbilical stump **AND** Newborn did not die on day 1	First applied CHX to umbilical stump after day 1 (regardless of neonatal outcome of baby)	**Newborns that Survived Neonatal Period:** Applied CHX to the umbilical stump on day 1 and applied it for less than 10 days **OR** stopped application before the cord separated (if the cord separated before day 10) **Newborns that did NOT Survive Neonatal Period:** Applied CHX to the umbilical stump on day 1 and applied it for less than 10 days **OR** they stopped before the day the cord separated (if the cord separated before day 10) **AND** they stopped applying CHX before the day the baby died	**Newborns that Survived Neonatal Period:** Applied CHX to the umbilical stump on day 1 and applied it for at least 10 days **OR** greater than or equal to the day that the cord separated **Newborns that did NOT Survive Neonatal Period:** Applied CHX to the umbilical stump on day 1 and applied it for at least 10 days **OR** greater than or equal to the day the cord separated **OR** until the day that the baby died; **OR** never applied CHX and baby died on day 1
Sunflower Oil	**Newborns that Survived Neonatal Period**: Did not apply sunflower oil **Newborns that did NOT Survive Neonatal Period:** Did not apply sunflower and baby died after day 3	**Newborns that Survived Neonatal Period:** Applied sunflower oil but stopped before day 7 (regardless of start date) **Newborns that did NOT Survive Neonatal Period:** Applied sunflower oil but stopped before day 7 (regardless of start date) and stopped using oil before the day that the baby died	**Newborns that Survived Neonatal Period:** First applied oil after day 3 and stopped applying it on at least day 7 **Newborns that did NOT Survive Neonatal Period:** First applied oil after day 3 and stopped applying oil on at least day 7 (but before day 14) and before the day that the baby died	**Newborns that Survived Neonatal Period:** First applied sunflower oil on or before day 3 **AND** stopped applying oil on day 7 or later **Newborns that did NOT Survive Neonatal Period:** First applied sunflower oil on or before day 3 **AND** applied oil until at least day 7 **OR** until the day baby died (if they died before day 7) **OR** Did not apply oil and baby died on or before day 3

		0	1	2	3
iNCK Component		**Never Used**	**Partial Compliance**	**Good Compliance**	**Excellent Compliance**
ThermoSpot (TS) Utilization		**Newborns that Survived Neonatal Period**: Did not use TS **Newborns that did NOT Survive Neonatal Period**: Did not use TS and baby did not die on day 1	**Newborns that Survived Neonatal Period:** First applied TS *after day 3* (irrespective of when they stopped); **OR** First applied TS on day 1 and stopped using it before day 4 (i.e., only 3 days of usage); **OR** First applied TS on day 2 or day 3 and stopped using it before day 6 or 7, respectively (i.e., only 4 days of usage) **Newborns that did NOT Survive Neonatal Period**: First applied TS on day 1 and stopped using it before day 4 (i.e., only 3 days of usage) and baby died after they stopped using TS; **OR** First applied TS on day 2 or day 3 and stopped using it before day 6 or 7, respectively (i.e., only 4 days of usage) and baby died after they stopped using TS	**Newborns that Survived Neonatal Period**: First applied TS on day 1 and stopped using it on or after day 4 (i.e., at least 4 days of usage that started on day 1); **OR** First applied TS on day 2 or day 3 and stopped using it on or after day 6 or day 7, respectively (i.e., at least 5 days of usage) **Newborns that did NOT Survive Neonatal Period**: First applied TS on day 1 and stopped using it on or after day 4 (i.e., at least 4 days of usage that started on day 1) and they died after they stopped using TS; **OR** First applied TS on day 2 or day 3 and stopped using it on or after day 6 or day 7, respectively (i.e., at least 5 days of usage) and they died after they stopped using TS; **OR** First applied TS on day 2 or day 3 and stopped using TS on the day baby died	**Newborns that Survived Neonatal Period**: First applied TS on day 1 and used it until at least day 7 **Newborns that did NOT Survive Neonatal Period**: First applied TS on day 1 and used it until at least day 7 or until the day they died; **OR** Did not use TS and baby died on day 1
Thermal Action	**Red: Moderate Hypothermia**	None of the following: Used heat pack Used blanket Sought health care	Any one of the following: Used heat pack Used blanket Sought health care	Any two of the following: Used heat pack Used blanket Sought health care	All three of the following: Used heat pack Used blanket Sought health care
	Black: Severe Hypothermia	None of the following: Used heat pack Used blanket Sought health care	Any one of the following: Used heat pack Used blanket Sought health care	Any two of the following: Used heat pack Used blanket Sought health care	All three of the following: Used heat pack Used blanket Sought health care
		0 - Never Used		**3- Excellent Compliance**	
	Pale Green: Cold Stress	Did not exercise Kangaroo care		Exercised Kangaroo care	
	Blue: Fever	Did not seek health care		Sought health care	

Table S3: Timing of consent collection and postnatal LHW visits

	Intervention	Control[b]	p value
Number of pregnant women who provided consent	2663	2788	---
GA at time consent collected (i.e., iNCK and/or standard of care delivered)[a], weeks			
Median, (min, max)	33 (17, 41)	36 (14, 42)	<0.0001
Time between iNCK and/or standard of care delivery and child birth, weeks			
Median, (min, max)	5 (1, 22)	3 (1, 38)	<0.0001
Number of pregnant women who received iNCK and/or standard of care:			
Less than 15 weeks before delivery, n (%)	2536 (96.8)	2684 (97.7)	0.03
Between 15 and 20 weeks before delivery, n (%)	79 (3.0)	48 (1.7)	0.03
More than 20 weeks before delivery, n (%)	48 (1.8)	56 (2.0)	0.65
LHW postnatal visits (self-reported by enrolled women)	1771 (80.1)		
Day 1	506 (28.6)	---	---
Day 2	539 (30.4)	---	---
Day 3	577 (32.6)	---	---
After day 3	149 (8.4)	---	---
Postnatal LHW teaching of iNCK components (self-reported by enrolled women)			
Chlorhexidine	1774 (80.2)	---	---
Sunflower oil emollient	1785 (80.7)	---	---
ThermoSpot	1790 (81.0)	---	---
Reflective blanket	1784 (80.7)	---	---
Heat pack	1785 (80.7)	---	---

[a]Gestational age, based on self-reported LMP, was calculated for 4573 participants, 2213 in the iNCK arm and 2318 in the standard of care arm. 130 and 89 participants in the iNCK and control groups, respectively, were enrolled into the study at a gestational age ≤ 27 weeks.
[b]Data pertaining to post-natal LHW visits in the control arm were not collected

Table S4: Timing and frequency of completed household data-collector visits by treatment group

	Intervention	Control	p value
Day first visit completed, n (%)			0.91
Day 1	289 (11.2)	259 (9.6)	
Day 2	879 (34.0)	927 (34.3)	
Day 3	1067 (41.3)	1152 (42.7)	
After Day 3	350 (13.5)	363 (13.4)	
Number of correctly[a] completed household visits during the neonatal period, n (%)			0.87
0 visits	350 (13.5)	363 (13.4)	
1 visits	5 (0.2)	2 (0.1)	
2 visits	23 (0.9)	24 (0.9)	
3 visits	13 (0.5)	29 (1.1)	
4 visits	1053 (40.7)	1129 (41.8)	
5 visits	1141 (44.1)	1154 (42.7)	

[a]To be considered as completed correctly, the first visit needed to happen within the first 3 days of life, the second visit needed to occur after day 2 but before day 7, the third visit had to occur after day 6 but before day 14, the fourth visit needed to occur after day 13 but before day 28, and the fifth visit needed to occur any time after day 27.

Table S5: Neonatal mortality by treatment group stratified by timing and frequency of data-collector home-visits

	Intervention	Control	Risk ratio (95% CI)	p value
0 home visits during first week of life				
Live births, n	338	357		
Newborn deaths, n	27	40		
Neonatal mortality rate (per 1,000 live births)	79.9	112.0	0.71 (0.43-1.18)	0.19
Age of newborn death (days), median (IQR)	1 (1, 2)	1 (1, 2)		
≥1 home visit during first week of life				
Live births, n	2219	2319		
Newborn deaths, n	38	42		
Neonatal mortality rate (per 1,000 live births)	17.1	18.1	0.95 (0.58-1.53)	0.82
Age of newborn death (days), median (IQR)	4 (3, 12)	5 (4, 14)		

Table S6: Neonatal mortality by treatment group stratified by timing of intervention and/or standard of care delivery

	Intervention	Control	Risk Ratio (95% CI)	p value
Intention-to-treat, complete case population				
Newborn mortality by timing of intervention and/or standard of care delivery				
Between 1 to 4 weeks before birth				
All live births, n	1022	1707		
Newborn deaths, n	18	44		
Neonatal mortality rate (per 1,000 live births)	17.6	25.8	0.68 (0.39-1.19)	0.18
Age of newborn death (days), median (IQR)	4 (2, 9)	4 (2, 14)		
Between 5 to 8 weeks before birth				
All live births, n	883	599		
Newborn deaths, n	31	20		
Neonatal mortality rate (per 1,000 live births)	35.1	33.4	1.05 (0.60-1.85)	0.86
Age of newborn death (days), median (IQR)	3 (1, 6)	2 (1, 4)		
Between 9 to 13 weeks before birth				
All live births, n	514	267		
Newborn deaths, n	11	10		
Neonatal mortality rate (per 1,000 live births)	21.4	37.5	0.57 (0.22-1.50)	0.26
Age of newborn death (days), median (IQR)	3 (2, 12)	1 (1, 3)		
Greater than 13 weeks before birth				
All live births, n	110	80		
Newborn deaths, n	2	5		
Neonatal mortality rate (per 1,000 live births)	18.2	62.5	0.29 (0.06-1.39)	0.12
Age of newborn death (days), median (IQR)	2 (1, 3)	1 (1, 3)		

Table S7: Neonatal mortality by treatment group stratified by gestational age at delivery

	Intervention	Control	Risk Ratio (95% CI)	p value
Intention-to-treat, complete case population				
Newborn mortality by GA				
Preterm Deliveries				
Live births born before 37 weeks gestation, n	415	445		
Newborn deaths, n	18	24		
Neonatal mortality rate (per 1,000 live births)	43.4	53.9	0.80 (0.45-1.44)	0.46
Age of newborn death (days), median (IQR)	4 (3, 8)	5 (3, 14)		
Deliveries ≥ 37 weeks gestation				
Live births born at ≥ 37 weeks gestation, n	1804	1874		
Newborn deaths, n	20	18		
Neonatal mortality rate (per 1,000 live births)	11.1	9.6	1.15 (0.57-2.35)	0.69
Age of newborn death (days), median (IQR)	9 (3, 13)	5 (4, 13)		

Table S8: Per-protocol effect of the iNCK on neonatal mortality by cut-off score used to define compliance

		Intervention	Control	
Cut-off Score (%)	**Participants per group[b] (n)**	**Deaths (n)**	**Deaths (n)**	**Relative Risk (95% CI)**
65	2124	27	41	0.66 (0.39-1.12)
75	2018	24	37	0.65 (0.37-1.13)
80	710	6	14	0.43 (0.17-1.08)
85	657	4	17	0.24 (0.08-0.70)
90	655	4	12	0.33 (0.11-1.03)
95	525	4	10	0.40 (0.13-1.25)
100	515	4	11	0.36 (0.12-1.10)
ITT	2557/2676[a]	65	82	0.83 (0.58-1.18)

[a]In the ITT analyses, there were 2557 participants in the kit group and 2676 participants in the control group.

[b]The number of participants that were included in these post-hoc per-protocol analyses was determined by the number of participants in the intervention group who met the given cut-off compliance score. These participants were compared to a 1:1 propensity-score matched control group based on maternal age, gravidity, total number of children alive, delivery location, antenatal care, and the number of antenatal care visits. The number of participants included in the intervention and control groups of these analyses were always equal.

Table S9: Per-protocol effect of the iNCK on neonatal mortality within the iNCK group by varying cut-off compliance scores

		Intervention Excellent Compliers	Intervention Non-excellent Compliers		
Cut-off Score (%)	**Participants per group (n)**	**Deaths (n)**	**Deaths (n)**	**Relative Risk (95% CI)**	**p value**
65[a]	95	2	11	0.18 (0.04-0.84)	0.03
75[a]	201	2	14	0.14 (0.03-0.67)	0.01
80	710	6	16	0.37 (0.14-0.99)	0.05
85	657	4	18	0.22 (0.08-0.63)	0.005
90	655	4	13	0.31 (0.10-0.99)	0.05
95	525	4	11	0.36 (0.11-1.17)	0.09
100	515	4	12	0.33 (0.11-1.00)	0.05

[a]At a compliance score cut-off of 65% and 75%, the 1:1 matched sample size was driven by the number of non-excellent compliers. All 1:1 propensity score matching was based on maternal age, gravidity, total number of children alive, delivery location, antenatal care, and the number of antenatal care visits

Table S10: Neonatal mortality by treatment group stratified by timing of first chlorhexidine (CHX) application

	Intervention			
	Applied CHX on day 1	**Applied CHX after day 1**	**Risk Ratio (95% CI)**	**p value**
Overall				
Live births, n	702	1494		
Neonatal deaths, n	9	20		
Neonatal mortality rate (per 1,000 live births)	12.8	13.4	0.96 (0.41-2.24)	0.92
Age of newborn death (days), median (IQR)	3 (3, 9)	6 (4, 18)		
Propensity Score Matched				
Live births, n	702	702		
Neonatal deaths, n	9	12		
Neonatal mortality rate (per 1,000 live births)	12.8	17.1	0.75 (0.28-1.98)	0.56
Age of newborn death (days), median (IQR)	3 (3, 9)	4 (4, 17)		

All 1:1 propensity score matching was based on maternal age, gravidity, total number of children alive, delivery location, antenatal care, and the number of antenatal care visits

Table S11: Neonatal mortality by treatment group stratified by clean birth kit utilization

	Intervention	Control	Risk Ratio (95% CI)	p value
Did not use a clean birth kit				
Live births, n	183	1148		
Neonatal deaths, n	1	26		
Neonatal mortality rate (per 1,000 live births)	5.5	22.6	0.24 (0.03-1.85)	0.17
Age of newborn death (days), median (IQR)	7 (7, 7)	5 (4, 12)		
Used a clean birth kit				
Live births, n	2036	1171		
Neonatal deaths, n	37	16		
Neonatal mortality rate (per 1,000 live births)	18.2	13.7	1.33 (0.73-2.41)	0.35
Age of newborn death (days), median (IQR)	4 (3, 12)	4 (3, 14)		

Table S12: Omphalitis within the intervention group stratified by timing of first application of chlorhexidine (CHX)

	Intervention			
	Applied CHX on day 1	**Applied CHX after day 1**	**Risk Ratio (95% CI)**	**p value**
Overall				
Live births, n	699	1504		
Any omphalitis, n (%)	32 (4.6)	68 (4.5)	1.01 (0.64-1.61)	0.96
Mild omphalitis, n (%)	29 (4.1)	61 (4.1)	1.02 (0.62-1.69)	0.93
Moderate omphalitis, n (%)	3 (0.4)	6 (0.4)	1.08 (0.37-3.11)	0.89
Severe omphalitis, n (%)	---	1 (0.1)	---	---
Propensity Score Matched				
Live births, n	699	699		
Any omphalitis, n (%)	32 (4.6)	32 (4.6)	1.00 (0.62-1.62)	1.00
Mild omphalitis, n (%)	29 (4.1)	28 (4.0)	1.04 (0.62-1.74)	0.89
Moderate omphalitis, n (%)	3 (0.4)	3 (0.4)	1.00 (0.26-3.82)	1.00
Severe omphalitis, n (%)	---	1 (0.1)	---	---

All 1:1 propensity score matching was based on maternal age, gravidity, total number of children alive, delivery location, antenatal care, and the number of antenatal care visits

Table S13: Omphalitis by treatment group stratified by place of delivery

	Intervention	Control	Risk Ratio (95% CI)	p value
OVERALL				
Live births, n	2225	2329		
Any omphalitis, n (%)	101 (4.5)	155 (6.7)	0.68 (0.48-0.98)	0.04
Any mild omphalitis, n (%)	91 (4.1)	133 (5.7)	0.72 (0.50-1.03)	0.07
Any moderate omphalitis, n (%)	9 (0.4)	25 (1.1)	0.38 (0.15-0.94)	0.04
Any severe omphalitis, n (%)	1 (0.0)	2 (0.1)	0.52 (0.05-5.74)	0.60
HOME DELIVERIES				
Live births, n	880	898		
Any omphalitis, n (%)	31 (3.5)	69 (7.7)	0.46 (0.27-0.78)	0.004
Any mild omphalitis, n (%)	26 (3.0)	63 (7.0)	0.42 (0.24-0.73)	0.002
Any moderate omphalitis, n (%)	4 (0.5)	8 (0.9)	0.51 (0.11-2.45)	0.40
Any severe omphalitis, n (%)	1 (0.1)	1 (0.1)	1.02 (0.06-16.25)	0.99
FACILITY DELIVERIES				
Live births, n	1345	1431		
Any omphalitis, n (%)	70 (5.2)	86 (6.0)	0.87 (0.59-1.28)	0.47
Any mild omphalitis, n (%)	65 (4.8)	70 (4.9)	0.99 (0.66-1.49)	0.95
Any moderate omphalitis, n (%)	5 (0.4)	17 (1.2)	0.31 (0.10-0.95)	0.04
Any severe omphalitis, n (%)	---	1 (0.1)	---	---

Table S14: Severe infection by treatment group stratified by place of delivery

	Intervention	Control	Risk Ratio (95% CI)	p value
OVERALL				
Any sign severe infection, n (%)	426 (19.1)	380 (16.3)	1.17 (0.80-1.72)	0.41
Convulsions, n (%)	1 (0.1)	2 (0.2)	0.51 (0.05-5.16)	0.57
Fast breathing, n (%)	23 (1.0)	41 (1.8)	0.59 (0.32-1.08)	0.08
Indrawing, n (%)	18 (0.8)	24 (1.0)	0.79 (0.40-1.53)	0.48
Fever, n (%)	83 (3.7)	136 (5.8)	0.64 (0.47-0.87)	0.004
Poor feeding, n (%)	363 (16.3)	292 (12.5)	1.30 (0.80-2.13)	0.29
Sign of abnormal activity level, n (%)	222 (10.0)	182 (7.8)	1.28 (0.75-2.17)	0.37
Any sign severe infection (remove poor feeding from SI definition)[a], n (%)	285 (12.8)	276 (11.9)	1.08 (0.76-1.55)	0.67
Any sign severe infection (remove abnormal activity from SI definition) [a], n (%)	415 (18.7)	372 (16.0)	1.17 (0.80-1.71)	0.43
Any sign severe infection (remove abnormal activity AND poor feeding from SI definition) [a], n (%)	112 (5.0)	174 (7.5)	0.67 (0.51-0.89)	0.006
HOME DELIVERIES				
Any sign severe infection, n (%)	288 (21.4)	256 (17.9)	1.14 (0.73-1.77)	0.57
Convulsions, n (%)	1 (0.1)	2 (0.2)	0.51 (0.05-5.11)	0.57
Cast breathing, n (%)	14 (1.0)	31 (2.2)	0.92 (0.36-2.33)	0.86
Indrawing, n (%)	6 (0.7)	9 (1.0)	0.68 (0.23-1.97)	0.48
Fever, n (%)	31 (3.5)	57 (6.3)	0.55 (0.37-0.84)	0.005
Poor feeding, n (%)	119 (13.5)	81 (9.0)	1.50 (0.80-2.82)	0.21
Sign of abnormal activity level, n (%)	74 (8.4)	47 (5.2)	1.61 (0.82-3.14)	0.16
Any sign severe infection (remove poor feeding from SI definition) [a], n (%)	96 (10.9)	92 (10.2)	1.06 (0.71-1.60)	0.76
Any sign severe infection (remove abnormal activity from SI definition) [a], n (%)	134 (15.2)	122 (13.6)	1.12 (0.72-1.75)	0.62
Any sign severe infection (remove abnormal activity AND poor feeding from SI definition) [a], n (%)	40 (4.5)	69 (7.7)	0.59 (0.41-0.85)	0.005
FACILITY DELIVERIES				
Any sign severe infection, n (%)	289 (21.5)	256 (17.9)	1.20 (0.81-1.78)	0.37
Convulsions, n (%)	2 (0.1)	2 (0.1)	1.06 (0.15-7.43)	0.95
Fast breathing, n (%)	14 (1.0)	31 (2.2)	0.48 (0.24-0.98)	0.04
Indrawing, n (%)	12 (0.9)	15 (1.0)	0.85 (0.37-1.96)	0.70
Fever, n (%)	52 (3.9)	79 (5.5)	0.70 (0.46-1.06)	0.09
Poor feeding, n (%)	244 (18.1)	211 (14.7)	1.23 (0.77-1.97)	0.39
Sign of abnormal activity level, n (%)	148 (11.0)	135 (9.4)	1.17 (0.69-1.96)	0.56
Any sign severe infection (remove poor feeding from SI definition) [a], n (%)	189 (14.1)	184 (12.9)	1.09 (0.74-1.61)	0.65
Any sign severe infection (remove abnormal activity from SI definition) [a], n (%)	281(20.9)	250 (17.5)	1.20 (0.81-1.77)	0.37
Any sign severe infection (remove abnormal activity AND poor feeding from SI definition) [a], n (%)	72 (5.4)	105 (7.3)	0.73 (0.50-1.07)	0.11

[a]In a post-hoc sensitivity analysis, poor feeding and abnormal activity were removed from the definition of severe infection; they are the least specific signs

References

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