Preventing Bloodstream Infections and Death in Zambian Neonates:

Impact of a Low-cost Infection Control Bundle

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Summary: Sepsis is a common cause of death among hospitalized neonates. A low-cost infection control bundle, including increased access to alcohol hand rub and weekly chlorhexidine baths, reduced rates of clinical sepsis, bloodstream infections, and death in most birthweight categories.

Abstract

Background. Sepsis is a leading cause of neonatal mortality in low-resource settings. As facility-based births become more common, the proportion of neonatal deaths due to hospital-onset sepsis has increased.

Methods. We conducted a prospective cohort study in a neonatal intensive care unit in Zambia where we implemented a multi-faceted infection prevention and control (IPC) bundle consisting of IPC training, text message reminders, alcohol hand rub, enhanced environmental cleaning, and weekly bathing of babies ≥1.5 kg with 2% chlorhexidine gluconate. Hospital-associated sepsis, bloodstream infection (BSI), and mortality (>3 days after admission) outcome data were collected for 6 months prior to and 11 months after bundle implementation.

Results. Most enrolled neonates had a birthweight ≥1.5 kg (2131/2669, 79.8%). Hospital-associated mortality was lower during the intervention than baseline period (18.0% vs 23.6%). Total mortality was lower in the intervention than prior periods. Half of enrolled neonates (50.4%) had suspected sepsis; 40.8% of cultures were positive. Most positive blood cultures yielded a pathogen (409/549, 74.5%), predominantly *Klebsiella pneumoniae* (289/409, 70.1%). The monthly rate and incidence density rate of suspected sepsis were lower in the intervention period for all birthweight categories, except babies weighing <1.0 kg. The rate of BSI with pathogen was also lower in the intervention than baseline period.

Conclusions. A simple IPC bundle can reduce sepsis and death in neonates hospitalized in high-risk, low-resource settings. Further research is needed to validate these findings in similar settings and to identify optimal implementation strategies for improvement and sustainability.

Clinical Trials Registration. NCT02386592

Key words: neonatal sepsis, mortality, *Klebsiella pneumoniae*, infection prevention, chlorhexidine, Zambia

Introduction

Approximately 2.7 million neonatal deaths occurred in 2015, accounting for 46% of all under-five child mortality [1]. Almost all (99%) neonatal deaths occur in low- and middle-income countries (LMICs) and about a fifth are attributable to neonatal sepsis and meningitis [2]. Bloodstream infections (BSIs), the most common hospital-associated infection in neonates, occur 3 to 20 times more frequently in LMICs than industrialized countries [3]. The excess burden of neonatal BSIs in LMICs is fueled by shortages of trained staff and basic resources, crowded clinical settings, malfunctioning equipment, increasing antimicrobial resistance and suboptimal infection prevention and control (IPC) practices [3,4].

Neonatal sepsis is a significant cause of morbidity and mortality in the largest referral neonatal intensive care unit (NICU) in Lusaka, Zambia (University Teaching Hospital, UTH). A recent study in this NICU found 43% mortality among septic neonates, predominantly due to multi-drug resistant *Klebsiella pneumoniae* [5]. IPC bundles composed of simple, relatively low-cost interventions [6,7] might reduce the incidence of BSI and neonatal mortality. To assess the effectiveness of low-cost measures in LMIC settings, we determined the incidence of hospital-associated neonatal sepsis and studied the impact of a novel IPC bundle on hospital-associated BSI and mortality among neonates in the UTH NICU.

Methods

We performed a prospective observational cohort study of neonates admitted to the NICU that included a six-month baseline period ("baseline"), 6 weeks of bundle implementation

("implementation"), and 11 months of intervention assessment ("intervention") (Supplemental Figure 1).

The study site, UTH, is a large tertiary care public hospital in Lusaka, Zambia, which is typically over-census (60 cots and an average daily census of 75 infants). There are ~3300 admissions per year. The average patient-to-nurse ratio is 20:1 (Appendix A contains additional information about the study site).

On weekdays from 8am to 5pm, study staff enrolled neonates admitted to the NICU from September 2015 through March 2017. For neonates admitted during evenings and weekends, enrolment was attempted the next working day. Neonates were excluded if their mothers were ≤18 years old unless a legal guardian ≥18 years of age gave consent for both mother and baby to participate.

The Boston University Medical Campus, ERES Converge (Zambia), Children's Hospital of Philadelphia Institutional Review Boards, the Zambian Ministry of Health Research Secretariat and the UTH Department of Pediatrics reviewed and approved the study. Written, informed consent was obtained from the neonate's mother or legal guardian in English or the most common local languages, Nyanja and Bemba. A data safety monitoring board, consisting of three independent experts in pediatrics, newborn health, and clinical trials in LMICs, met twice during the course of the study; no concerns were identified.

Study outcomes and definitions

The primary outcome was all-cause mortality among neonates hospitalized at UTH NICU ≥3 days ("hospital-associated mortality") to ensure that enrolled babies were exposed to the NICU-based interventions. Secondary outcomes included incidence of hospital-associated (onset ≥3 days after NICU admission) suspected sepsis and BSIs.

Blood cultures were obtained on all neonates with clinically suspected sepsis, defined as fever or hypothermia, tachycardia or bradycardia, hypoglycemia, respiratory difficulty, new onset seizures, lethargy, poor feeding, abdominal distention, vomiting, diarrhea, or poor perfusion**.**

Positive blood cultures were classified as either BSI with pathogen or BSI with contaminant organism using commonly accepted criteria [8,9]. Appendix A contains additional description of classification of infants who experienced multiple episodes of suspected sepsis.

IPC interventions

Our IPC bundle included: 1) IPC training; 2) locally manufactured alcohol hand rub; 3) weekly bathing with 2% aqueous chlorhexidine gluconate (CHG; Clorox Company, Oakland, CA); 4) daily IPC reminders via short messaging service (SMS); and 5) enhanced routine cleaning of the environment including potential reservoirs of infection (e.g. sinks and suction machines) with a focus on daily cleaning of high-touch surfaces and moving from clean to dirty. We did not introduce any changes in the cleaning and disinfection products used.

The IPC training was developed based on JHPIEGO's curriculum [10]. Two identical trainings were held, over 2 consecutive half-days. Study team members (C.P., S.C., C.L., J.M., M.B) taught all modules. Break-out sessions focused on role-specific practices (e.g. environmental disinfection for cleaners, CHG bathing for nurses).

Alcohol hand rub was made according to a WHO-recommended formulation for local production [11]. The NICU pharmacist oversaw production and ensured that continual availability. Hand rub dispensers were either wall-mounted or on mobile stands. Two dispensers were positioned in strategic locations close to patient care in all rooms. Study personnel performed daily checks of dispensers and replaced empty containers as necessary. Posters promoting and demonstrating proper technique for the WHO Five Moments of Hand Hygiene were prominently displayed.

All enrolled neonates admitted during the implementation and intervention periods underwent CHG bathing (sparing head and face) at admission and weekly thereafter unless they met an exclusion criteria: severe skin disease, an open wound, birthweight <1.5 kg, or estimated gestational age <32 weeks. Once newborns achieved both a weight of ≥1.5 kg and corrected gestational age of ≥32 weeks, they were eligible for CHG bathing, criteria currently used by many U.S. NICUs [12].

During the intervention period, daily SMS messages designed to reinforce IPC practices and concepts taught in the training sessions were sent to all NICU staff once daily. The messages included reminders on hand hygiene, appropriate glove use and peripheral catheter care, and

urged staff to reassess the duration and need for indwelling catheters. Additional description of the implementation of these interventions is provided in Appendix B.

Data collection

Prospective data: At enrolment, study staff interviewed mothers and reviewed maternal medical records to identify perinatal exposures, such as HIV status and prenatal infections. No observational data were collected on hand hygiene, environmental cleaning, or other IPC practices due to limited study staffing.

Historical data: Using multiple sources, we assembled a limited data set to describe comprehensive neonatal mortality at the study NICU prior to study initiation. Limited data on all admitted neonates from October 2014 to March 2017 were extracted from the unit's discharge log, which was maintained by the unit clerk and completed at the time of each baby's discharge or death. The log included dates of admission and discharge, birthweight, admission diagnoses, and vital status at discharge. Additionally, we captured similar data from a prior study's database from June 2013 to September 2014 [5]. See Appendix A for additional description of analysis of historical data.

Microbiology data: One blood culture was obtained on all neonates with clinically suspected sepsis at the time of symptom onset. Urine and cerebrospinal fluid cultures were rarely obtained. Typically, a second blood culture was obtained if a patient developed a new episode of suspected

sepsis. Pediatric blood culture bottles were inoculated with 0.5-1.0 ml of blood and incubated in the BD Bactec® blood culture system (BD Life Sciences; Franklin Hill, NJ). Organisms isolated were tested for antibiotic susceptibilities using the VITEK® Compact 2 ID/AST automated machine (bioMerieux, Durham, NC).

Data management and analysis

Prospective data were collected by full-time study staff into an electronic data collection platform implemented on electronic tablets (SurveyCTO, Cambridge, MA). Data were downloaded into SAS v.9.4 (Cary, NC) and STATA v.15.1 (College Station, TX) on a secure server.

Our pre-specified analytic plans included aggregating data by month and constructing three discrete time periods (baseline, implementation, and intervention) for descriptive and statistical comparisons. Enrolled neonates were characterized by maternal demographic and clinical characteristics, neonatal clinical characteristics, and outcomes. Clinicaltrials.gov registration number NCT02386592.

Prospective data: We evaluated the effect of the study intervention on hospital-associated mortality and secondary outcomes of hospital-associated suspected sepsis, BSI with pathogen, or BSI with contaminant.

We used a simple piecewise regression with time as the covariate of interest, and with two knots to reflect possible discontinuity in the rates at the start of the implementation (month 7) and

intervention (month 9) periods. We examined the change in levels and trajectories of hospital-associated mortality as well as our secondary outcomes over time.

Monthly rates of mortality and BSI-pathogen were examined among study participants. Smoothed rates were also calculated using a standard smoother for exploratory data analysis to reduce noise.[13]

Microbiological data: All blood cultures which grew one or more organisms were included in this analysis. Blood cultures which grew two or more organisms were classified as polymicrobial; if both a pathogen and a common skin commensal (contaminant) were isolated from the same culture, it was designated as BSI with pathogen.

Sensitivity analysis

We conducted a sensitivity analysis to determine the impact of unmeasured confounders on observed mortality using "E-values". The E-value determines how large an unmeasured confounder must be in order to negate the observed effect of the intervention (Appendix B) [14].

Results

Of 3686 newborns screened, 3348 (90.8%) were enrolled but only 2669 were fully evaluable, primarily due to death prior to day three of hospitalization in the study NICU (Figure 1).

The median maternal age and proportion of HIV-positive mothers were similar in all three time periods (Table 1). There were no differences in newborn characteristics in the three time periods with the exception of birthweight. There were no adverse events associated with CHG bathing.

Hospital-associated mortality

Overall hospital-associated mortality for enrolled neonates was 20.1% and was lower during the intervention (18.0%) than the baseline (23.6%) period. Hospital-associated mortality was lowest for neonates >2.5 kg and highest in neonates <1.0 kg (Table 2). Hospital-associated mortality declined from baseline to intervention periods in all birthweight categories.

Total Mortality

We compared the historic monthly mortality data to the total mortality (early and hospital-associated) during the intervention period (Figure 2A) and observed reduced rates of total mortality during the intervention period. When stratified by calendar month, the absolute mean monthly mortality reduction was -9.1 percentage points (95% CI= -10.8 to -7.3) and the overall reduction in relative mortality was 21.0% (RR = 0.79; 95% CI=0.76 to 0.83). Heterogeneity of mortality reduction by calendar month was limited, with relative mortality ranging from 0.64 to 0.95 during the intervention period.

Suspected sepsis and bloodstream infection

Half of the enrolled neonates (1344/2669, 50.4%) experienced one or more episodes of suspected sepsis. The monthly rate of suspected sepsis was lower in the intervention than baseline period

(Figure 2B). Similarly, incidence density rates for suspected sepsis were lower during the intervention than baseline period for all birthweight categories, except babies <1.0 kg (Table 3A).

Fewer than half of episodes of suspected sepsis (549/1344, 40.8%) were associated with a positive blood culture and the proportion of neonates with a positive blood culture was inversely associated with birthweight category. Pathogens were isolated from most positive blood cultures (409/549, 74.5%). The most frequently isolated pathogens were *K. pneumoniae* (289/409, 70.1%) and *Enterococcus* spp. (70/409, 18.6%). The rate of BSI with pathogen was higher for babies of all birthweights in the baseline than the intervention period (Figure 3). Similarly, the incidence density rate of BSI with pathogen was higher for all birthweight categories during the baseline than the intervention period, except for neonates <1.0 kg (Table 3B).

The daily hazard of death and BSI varied by duration of NICU stay and study period (Supplemental Figure 2). The daily hazard of death was lower during the 1st week of hospitalization in the intervention than baseline period. In contrast, the daily hazard of BSI with pathogen was highest on NICU day three (1st day of study observation) for all babies, but lower for babies hospitalized during the intervention than the baseline period.

As a sensitivity analysis, we estimated the magnitude of unmeasured confounding, not already accounted for by our measured factors and design, needed to negate our observed association (RR=0.79) between our intervention and hospital-associated mortality. Such a confounder would need to be associated with our intervention and mortality by the same relative risk of ≥1.85, and not lower. A confounder with less strong associations could not explain away this mortality

reduction. We cannot identify such a strong unmeasured factor or a differential exposure that might account for the observed association. Additional sensitivity analysis, their interpretation, and the reference for the calculations appear in Appendix C.

Discussion

There were significant reductions in the rates of suspected sepsis, BSI, and mortality among neonates in a low-resource NICU following implementation of a low-cost IPC bundle. We found lower rates of total and hospital-associated neonatal mortality after implementation of the IPC bundle. Additionally, we observed that hospital-associated mortality decreased across all birthweight groups, although the reductions were greatest among neonates <2.5 kg. These findings are similar to observations made in a study performed in two NICUs in Manila, Philippines where a simpler bundle (composed of introduction of locally produced alcohol based hand rub, IPC training and checklists) reduced overall neonatal mortality [6].

We observed reductions in the rates of sepsis and BSI with pathogen across all birthweight categories except neonates <1.0 kg. Early deaths due to extreme prematurity and difficulties obtaining a sample for blood culture might have contributed to this finding. Prior quasi-experimental studies of the capacity of a simple IPC bundle to prevent neonatal sepsis have yielded inconsistent results [6,15]. Our data suggest that the observed mortality reductions were potentially achieved by reducing mortality among all neonates (both those who did and did not experience sepsis), as well as by reducing sepsis. Our crude mortality analysis suggests that our intervention may have dampened the apparent seasonal variation with elimination of the peaks associated with the dry season. While the mechanism by which this change might have been exerted is unclear, this finding deserves future study.

Our low-cost IPC bundle included both evidence-based and novel interventions. Practices such as staff education, hand hygiene, and environmental cleaning, are well-recognized facets of IPC practice in both resource advantaged and limited settings [16,17]. In contrast, few published studies from LMIC hospitals have described the use of CHG bathing as a strategy to prevent sepsis or death. Studies performed in South Africa and Pakistan found that CHG bathing was not associated with a reduced rate of neonatal sepsis or death, although the concentration of CHG used in these studies was lower than used in our study (2% vs. <1%) [18] [19]. Studies from North America have described the impact of daily CHG bathing on rates of bacteremia and infection with multidrug-resistant organisms in children and adult patients with central venous catheters [20,21]. Among non-hospitalized neonates, the use of CHG for cord care is associated with reduced rates of omphalitis, neonatal sepsis, and death in some, but not all, settings [22–26]. Although reported in other studies, we did not observe adverse events (such as skin irritation) in neonates exposed to CHG [27].

While numerous studies have described the impact of a single intervention (e.g. staff education or introduction of alcohol hand rub) on colonization and neonatal sepsis, few studies have evaluated the impact of a bundle of IPC interventions. Prior reports have mainly focused on the control of outbreaks in LMIC NICUs and have often lacked detail on the interventions [28]. Additionally, few studies performed in NICUs have assessed the impact of IPC interventions on hospital-associated mortality.

Given evidence of impact of the interventions, the relative simplicity and potential for sustainability of our IPC bundle merit highlighting. Alcohol hand rub was produced locally

through using relatively inexpensive reagents. CHG was externally procured (at low cost) for neonatal bathing. Daily IPC reminders via SMS using customized messages for different cadres of NICU clinical and non-clinical personnel may have enhanced adherence to specific elements of our IPC bundle such as hand hygiene at low cost. Similarly, mobile technology-based health interventions have shown improved health worker behaviors for initiatives as diverse as acute respiratory infection and malaria case management [29,30].

Our study design did not allow a rigorous analysis of the relative contribution of individual bundle components. Such an analysis would require larger numbers of patients and an extended study period. Future studies are needed to dissect whether more financial and labor-intense interventions (such as CHG bathing) are necessary to achieve maximal benefit.

Strengths of our study include the availability of robust historical data, use of low cost interventions with locally available supplies, ability to control for or at least identify alternative explanations for our findings, and longitudinal data collection over sufficient time to account for seasonal variation. There are also several important limitations. First, as a prospective observational, single site study, our findings may not be easily generalizable. However, a randomized trial of unit-level interventions would require many NICUs to achieve an adequate sample size. This was beyond the scope of our funding. Second, we were unable to enroll participants on weekends and during public holidays due to limited staff availability, although we have no evidence that weekend/holiday admissions fare differently than those enrolled in our study. Similarly, with available research personnel we were unable to capture detailed data on babies who died or were discharged within three days of NICU admission. Third, adherence to study interventions, including hand hygiene and environmental cleaning, could not be

systematically assessed. This study was pragmatic, and as such generalizes to typical settings that might face imperfect adherence. Finally, we were unable to assess the sustainability of the observed benefits of the interventions. Although our interventions were selected based upon the relative low cost and ease of implementation, they did require supplemental resources such as dedicated effort from the hospital pharmacy (to produce and distribute the alcohol-based hand rub and CHG) and modest costs associated with purchase of CHG and use of text reminders. As future studies seek to reproduce these findings, they should assess the costs associated with these interventions. It will also be essential to determine how these individual interventions can be embedded in hospital operations and funded through routine budgeting to ensure sustainability.

In conclusion, we observed a reduction in neonatal sepsis and death associated with the implementation of an IPC bundle. Many NICUs and special care nurseries in resource-limited settings have serious limitations in space, staffing, and funding that challenge implementation of many traditional IPC measures, such as cohorting, isolation, and surveillance cultures. Thus, low-cost bundled interventions may represent the most effective and sustainable measures to prevent neonatal sepsis and death in these settings.

Notes:

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Potential conflicts of interest: S.E.C. serves on a Data Safety and Monitoring Board for Merck & Co. All other authors have no conflicts of interest to declare.

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Table 1: Characteristics of enrolled mothers and neonates in the neonatal intensive care unit (n=2669)

	Baseline N=852	Implementation N= 268	Intervention N= 1549	Significance[1]
Mother				
Median age, years (IQR)	25 (21-31)	24 (20-31)	25 (21-31)	p=0.44
HIV status				
Positive	167 (20%)	59 (22%)	320 (21%)	p=0.83
Negative	622 (74%)	207 (78%)	1219 (79%)	
Unknown	63 (7%)	2 (0.7%)	6 (0.4%)	
Neonate				

Birth weight				
<1.0 kg	12 (1%)	6 (2%)	48 (3%)	p<0.001
1-1.49kg	141 (17%)	40 (15%)	291 (19%)	
1.5-2.49kg	249 (29%)	92 (34%)	516 (33%)	
≥ 2.5kg	450 (53%)	130 (49%)	694 (45%)	
Mode of delivery				
Spontaneous vaginal delivery	648 (77%)	198 (74%)	1162 (75%)	p=0.92
Spontaneous vaginal delivery with instrumentation	9 (1%)	8 (3%)	51 (3%)	
Caesarean section	189 (22%)	61 (23%)	330 (21%)	
Unknown	6 (0.7%)	1 (0.4%)	6 (0.4%)	

[1] Comparing baseline to intervention period

Table 2: Hospital-associated mortality by birth weight category

Birth weight category	Baseline			Implementation			Intervention			Total		
	N	No. Died	%	N	No. Died	%	N	No. Died	%	N	No. Died	%
< 1 kg	10	9	90.0	6	5	83.3	46	36	78.3	62	45	80.4
1-1.49 kg	141	74	52.5	40	22	55.0	291	89	30.6	472	185	39.2
1.5-2.49 kg	249	55	22.1	92	10	10.9	516	69	13.4	857	134	15.6
≥ 2.5 kg	450	62	13.8	130	19	14.6	694	85	12.3	1274	166	13.0
TOTAL	852	201	23.6	268	56	20.1	1549	279	18.0	2669	536	20.1

Table 3A: Incidence density rate (per 100 patient days) of suspected sepsis by birth weight categories.

Birth weight category	Baseline	Intervention	Incidence rate ratio (95% CI^)	Significance
< 1kg	3.57	4.92	1.38 (0.53-4.57)	p =0.53
1-1.49 kg	7.09	3.42	0.48 (0.37-0.62)	p<0.001
1.5-2.49 kg	8.07	5.06	0.63 (0.51-0.77)	p<0.001
≥2.5 kg	9.15	5.95	0.65 (0.55-0.76)	p<0.001

^CI = confidence interval

Table 3B: Incidence density rate (per 100 patient days) of BSI-pathogen by birth weight categories.

Birth weight category	Baseline	Intervention	Incidence rate ratio (95% CI^)	Significance
< 1kg	2.86	1.76	0.62 (0.18-2.69)	p =0.42
1-1.49 kg	3.74	1.03	0.28 (0.18-0.42)	p<0.001
1.5-2.49 kg	3.27	1.25	0.38 (0.26-0.55)	p<0.001
≥2.5 kg	3.02	1.43	0.47 (0.35-0.65)	p<0.001

^CI = confidence interval

Figure Legends:

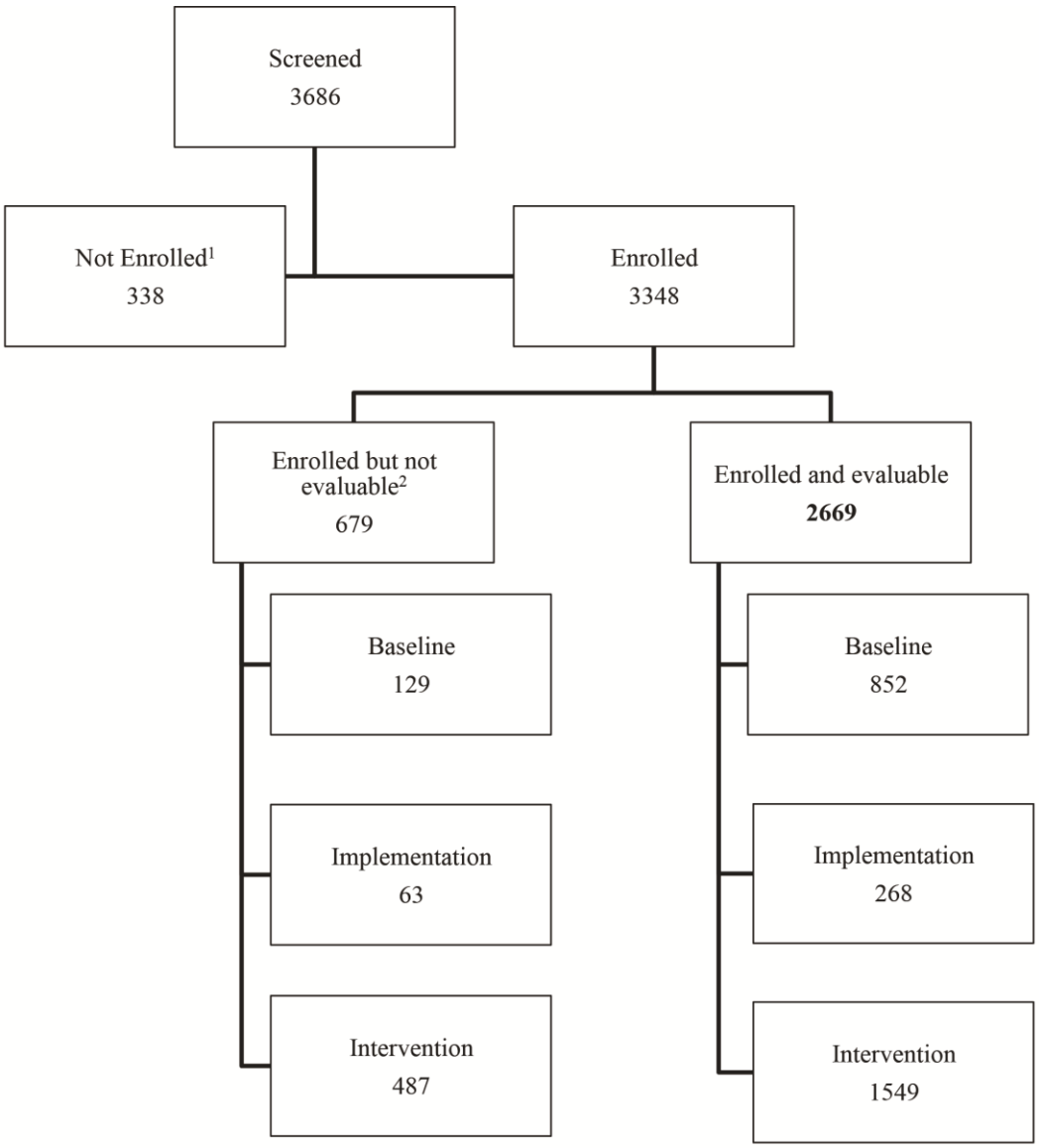
Figure 1: Assembly of study cohort.

Figure 2A: Overall (early and hospital-associated) crude mortality rate of patient-days at risk grouped by month of admission to the NICU (dots). Smoothed mortality rates (line) reflect standard smoother for exploratory data analysis. Seasonal variation was pronounced prior to the intervention compared to after the intervention.

Figure 2B: Crude monthly rate of suspected sepsis (dots) and smoothed monthly rate (line) of patient-days at risk grouped by month of admission to the NICU among enrolled neonates admitted to the UTH NICU from September 2015 through March 2017.

Figure 3: Proportion of enrolled neonates without sepsis, with culture negative sepsis, BSI due to pathogen (BSI-pathogen) and BSI due to possible contaminant (BSI-contam) stratified by intervention and birth weight.

Figure 1



[1] Unavailable to provide consent due to early death or discharge

[2] Died prior to NICU day three (670) or missing study maternal-neonatal and/or completion form (9)

Figure 2A

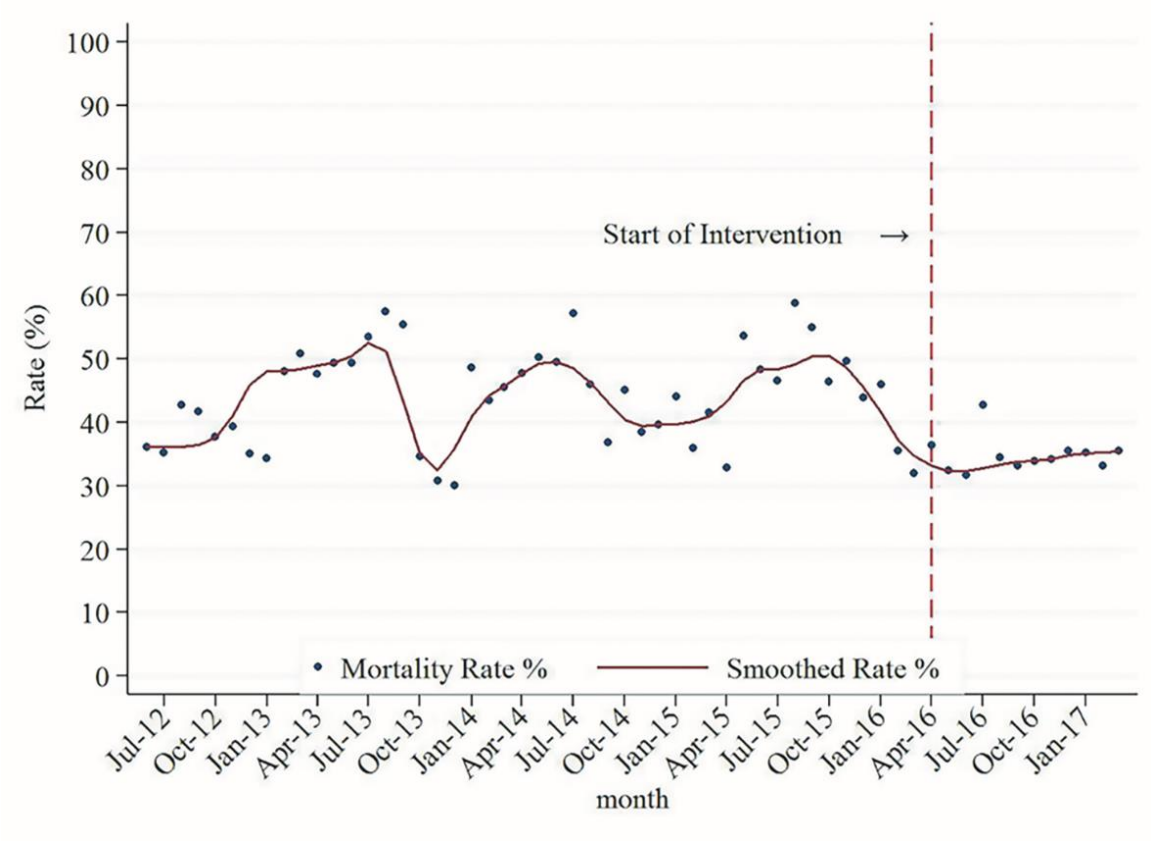


Figure 2B

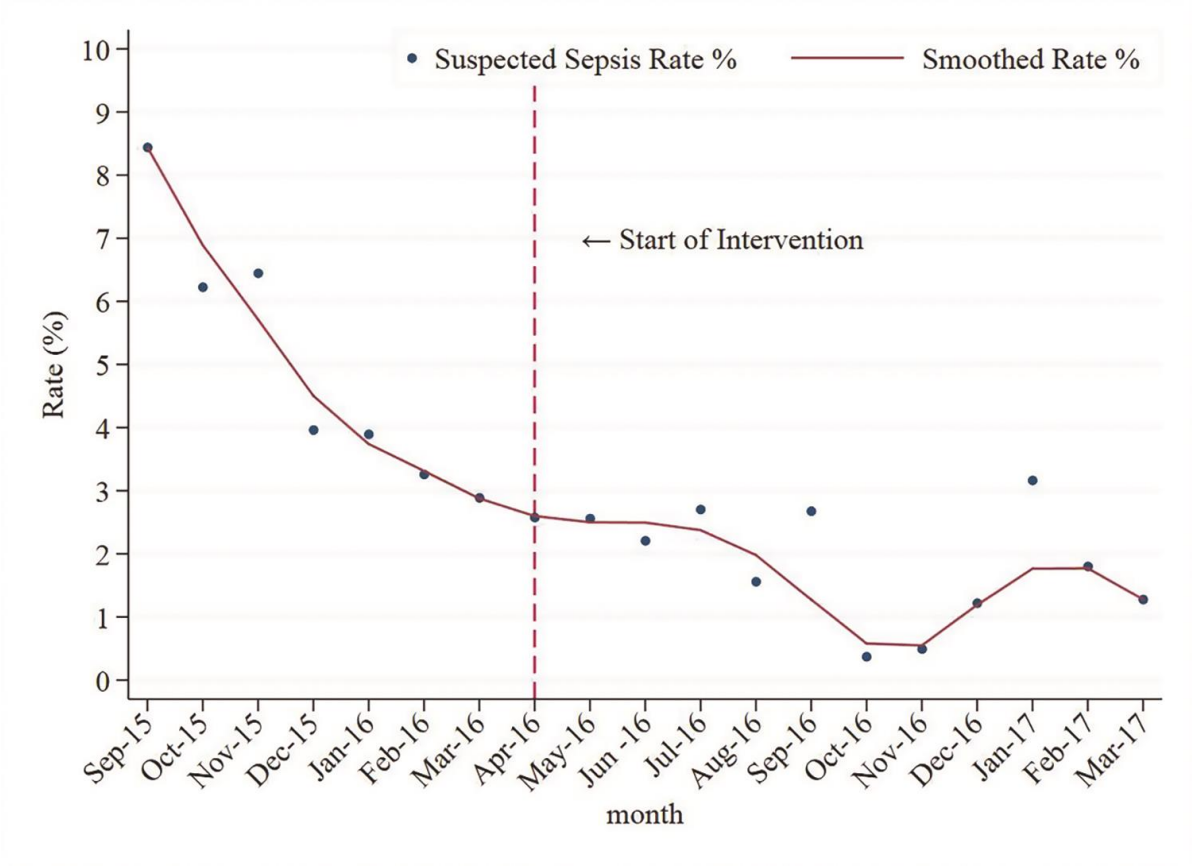


Figure 3