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Neonatal health in low- and middle-income countries

Edited by
Britt Nakstad, Ashish K. C., Andrew Steenhoff
and Susan Coffin

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Neonatal health in low- and middle-income countries

Topic editors
Britt Nakstad — University of Botswana, Botswana
Ashish K. C. — University of Gothenburg, Sweden
Andrew Steenhoff — Children's Hospital of Philadelphia, United States
Susan Coffin — University of Pennsylvania, United States

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EDITED BY
Eugene Dempsey,
University College Cork, Ireland

*CORRESPONDENCE
Britt Nakstad
✉ britt.nakstad@medisin.uio.no;
✉ nakstadb@ub.ac.bw

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Editorial: Neonatal health in low- and middle-income countries. Now is the time

Andrew P. Steenhoff[1,2,3,4], Susan E. Coffin[1,2,3], Ashish KC[5,6] and Britt Nakstad[4,7]*

[1]Global Health Center & Division of Infectious Diseases, The Children's Hospital of Philadelphia, Philadelphia, PA, United States, [2]Department of Pediatrics, University of Pennsylvania, Philadelphia, PA, United States, [3]The Botswana-UPenn Partnership, Gaborone, Botswana, [4]Department of Paediatric & Adolescent Health, Faculty of Medicine, University of Botswana, Gaborone, Botswana, [5]School of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [6]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden, [7]Division of Paediatric and Adolescent Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

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Editorial on the Research Topic
Neonatal health in low- and middle-income countries. Now is the time

The first 28 days after birth—the neonatal period—is the most vulnerable month for a child (1). The global "Every Newborn" action plan, which was endorsed by the WHO General Assembly in 2014, sets out an ambitious vision of a world with no preventable stillbirths or neonatal deaths (2). The action plan, endorsed in 2014 by 194 member states, articulates a goal that all countries reach the target neonatal mortality rate (NMR) of 12 or less newborn deaths per 1,000 live births by 2030, as well as commit to ongoing work to reduce death and disability. Achieving this interim goal is essential to ensure that no newborn is left behind. This metric was adopted as a target for Sustainable Development Goal (SDG) Target 3.2 (3). Despite a decline of more than 50% in the global neonatal mortality between 2000 and 2021, 2.4 million neonatal deaths still occur each year. The majority (79%) of these deaths take place in countries in South Asia and Sub-Saharan Africa, where the social system and health care settings are inadequately resourced.

This editorial team was pleased to use this special issue as an opportunity to identify new frontiers in global neonatal health, especially in the context of two global crises—the SARS-CoV-2 pandemic and climate change. We received 65 manuscripts, of which 40 (62%) were accepted. These 40 included 27 (68%) original research manuscripts, five (13%) brief research reports, three (8%) perspective pieces, two (5%) reviews, one (3%) case report, one (3%) on hypothesis and theory, and one (3%) on methods. First authors represented 15 countries; six in Africa (Botswana, Ethiopia, Nigeria, South Africa, Tanzania, Uganda), five in Asia (Bangladesh, China, India, Japan, Malaysia), three from Europe (Sweden, Switzerland, United Kingdom) and one in North America (United States). Of the 40 accepted papers the countries with the most first authors were South Africa (8; 20%), United States (7; 18%) and Ethiopia (5; 13%). Issues related to suboptimal study design or biostatistical analysis led to the rejection of 25 submitted papers.

Multiple factors influence neonatal health in LMIC, so a broad range of topics were included. High-risk preterm neonates in China were followed more effectively in a family-centred, child-friendly multidisciplinary clinic, leading to an earlier diagnosis of neurodevelopmental impairment and cerebral palsy (Huang et al.). In Ethiopia, less than 10% of neonates received post-natal check-ups. Increasing antenatal care (ANC) visit utilization, improving institutional delivery, raising awareness about neonatal danger signs, increasing access to health care facilities, and implementing home-based neonatal care visits by healthcare providers could all help to improve postnatal check-ups (Birhane et al.).

The Every Mother Every Newborn (EMEN) tools can reasonably measure WHO/UNICEF/UNFPA quality standards (Siseho et al.). In India, the quality and impact of home visitation services remains challenging and can be enhanced by addressing the social-cultural, organizational, educational, economic, and physical nexus domains with concurrent efforts for skill and confidence enhancement of the Accredited Social Health Activists (ASHAs) and their credibility (4).

Most mothers in rural Ethiopia had limited knowledge of Early Newborn Care (ENC). There is opportunity to enhance maternal knowledge pertaining to cord care, breastfeeding, and thermal care by improving access to ANC and institutional delivery (Siseho et al.). In Bangladesh there is room for improvement of the entire maternal care continuum—from ANC to facility delivery and postnatal care (PNC) to improve care-seeking for the sick newborn. Strategies such as referral training for unqualified providers, targeted intervention for poorer households, increasing community health care worker (CHW) home visits and neonatal danger sign counselling at the facility and community could address these issues in many LMIC (Getachew et al.; Azad et al.).

A number of papers explored aspects of Kangaroo Mother Care (KMC). In a neonatal cohort from South Africa, both HIV-exposed uninfected and HIV unexposed uninfected groups of infants showed reasonable weight gain regardless of maternal HIV status (Getachew et al.). In Uganda implementation of KMC has been suboptimal, despite wide acceptance (Azad et al.), highlighting post-discharge challenges in rural and resource-limited settings. The study provided insights on KMC implementation and sustainability from the perspectives of key stakeholders, highlighting the need for a holistic approach to KMC that incorporates its adaptability to community settings and contexts. Gambian researchers demonstrated the impact of health system limitations on successful delivery of KMC, and suggested that linkage to comprehensive health care worker (HCW) and KMC provider education would enhance effectiveness, safe delivery and monitoring (Mapatha et al.). Further context specific research into safe and respectful implementation is required from varied settings and should include perceptions of all stakeholders, especially if there is a shift in global policy toward KMC for all small vulnerable newborns (Mapatha et al.; Kwesiga et al.; Cho et al.).

As LMIC health systems continue to advance, the complexity of care also increases. One example is the correction of complex birth defects such as bladder exstrophy (BE). BE requires a complex, long-term course of care and in India this significantly impacted caregiver distress (Spencer et al.). Mental health screening for caregivers of children with complex congenital anomalies like BE, should be an essential element of any comprehensive effort to alleviate the global burden on mothers and families of neonates born with congenital anomalies.

Newborn nutrition is crucial. Feeding practices for very preterm and VLBW infants vary widely within Nigeria and Kenya, likely because of lack of locally generated evidence. High quality research that informs the feeding of these infants in the context of limited human resources, technology and consumables is urgently needed (Tongo et al.). Vitamin insufficiency should be checked (Wang et al.) as well as awareness of maternal undernutrition (Bilal et al.) and poor neonatal care in conflict settings (Kampalath et al.).

Health systems strengthening at all levels and quality improvement work is needed to improve global neonatal health and reduce death rates. Factors influencing neonatal mortality, morbidity and outcomes (Ramdin et al.; Ingemyr et al.; Shiferaw et al.; Mokuolu et al.; Adugna and Worku; McCulloch et al.) were discussed in several papers, especially preterm babies (Mangiza et al.; Hailemeskel and Tiruneh) as well as a need to optimize treatment of respiratory distress syndrome with appropriate and affordable non-invasive equipment (Ekhaguere et al.). Several studies examined factors associated with poor neonatal outcome, emphasizing that the quality of newborn care around the time of birth and prior to discharge is essential. In South Africa's largest hospital almost one-third of babies born by Caesarian section develop moderate (27%) or severe (2%) hypothermia (Siseho et al.; Patel et al.). Poor outcomes may also follow discharge against medical advice (DAMA). In China, the rate of DAMA in preterm infants remains high (14%) with a significant impact on neonatal mortality rates (Xiu et al.). Continuous efforts to reduce hypothermia after Caesarian delivery and minimize neonatal DAMA would likely result in substantial improvement of outcomes for infants in many parts of the world. It is essential to have available locally-appropriate technologies to avoid hypothermia after birth (5) as well as enable effective screening of neonatal jaundice (Suzuki et al.). To reduce risk of complications of neonatal hypoxic ischemic encephalopathy in LMIC, hypothermia treatment is warranted but challenging to perform [Birhane et al. (5), Boo et al.]. Other papers emphasized the need for newborn resuscitation training with video-recording (Olson et al.), and that intramuscular epinephrine in a neonatal animal model (Berkelhamer et al.) was not effective. Training of NICU staff is important to strengthen basic neonatal care practises (Swanson et al.), not least when the ward is understaffed and overcrowded. Complications of prematurity as well as congenital conditions and options for adequate treatment in LMIC were discussed in various papers (Spencer et al.; Xiu et al.; Kesting and Nakwa; Vidavalur; Liu et al.). Last, but not least, several papers focused on neonatal infection prevention, antibiotic stewardship, antibiotic resistance patterns (Johnson et al.; Holgate et al.; Shah et al.), and infectious diseases that are more common in warm climate LMICs (Mapatha et al.; Nakstad et al.; Nakwa et al.; Sundararaman and Odom John).

We wish to highlight ongoing challenges of achieving scientific equity for work being done in LMIC. Ensuring that physicians, scientists, and policy makers from all parts of the globe have easy access to these publications was essential to our editorial team. While open access publications achieve this "access" goal, we acknowledge that publication fees represent a barrier to many scientific authors. This barrier disproportionately affects authors from LMICs who have less access to research funding. This in turn perpetuates a systemic publication bias in favour of data from high-income countries (HIC) and stunts science in LMICs. We encourage journals to find the sweet spot of open access, affordability for authors and journal financial sustainability. An excellent example of how this might be accomplished is the recently launched Journal of African Neonatology (6). This biannual peer-reviewed open-access journal published by the African Neonatology Association accepts and publishes manuscripts in English and French with a publication fee of US $50. Indeed, now is the time for major progress in neonatal health in LMIC.

We also acknowledge that this research topic only accepted manuscripts in English favouring some authors but placing many at a linguistic disadvantage. A number of papers benefitted from detailed copy editing by generous, dedicated reviewers and we acknowledge and sincerely thank them for their contributions towards scientific equity.

This collection of articles is timely, inspiring, informative, and crucial, but given the grand scope and pressing nature of the topic, incomplete. With an eye to the future, we hope that this collection will be part of a "publication shift" where many future research topics will be dedicated to neonatology in LMIC and that journals will increasingly focus on highlighting scholarship to advance neonatal care in LMIC. Guided by expert opinion and evidence for equitable partnerships in global child health [Steenhoff et al. (7)], let us each play our role in advancing the care of neonates in LMIC.

Author contributions

All authors were part of the Editorial board of the Research Topic of Neonatal Health in Low- and Middle-Income Countries. All were editing and reviewing manuscripts in the research topic, contributed to writing and accepting the final version of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Implementation of the Comprehensive Unit-Based Safety Program to Improve Infection Prevention and Control Practices in Four Neonatal Intensive Care Units in Pune, India

Julia Johnson[1,2]*, *Asad Latif*[3,4], *Bharat Randive*[5], *Abhay Kadam*[5], *Uday Rajput*[6], *Aarti Kinikar*[6], *Nandini Malshe*[7], *Sanjay Lalwani*[8], *Tushar B. Parikh*[9], *Umesh Vaidya*[9], *Sudhir Malwade*[10], *Sharad Agarkhedkar*[10], *Melanie S. Curless*[11], *Susan E. Coffin*[12], *Rachel M. Smith*[13], *Matthew Westercamp*[13], *Elizabeth Colantuoni*[14], *Matthew L. Robinson*[15], *Vidya Mave*[5,15], *Amita Gupta*[15], *Yukari C. Manabe*[15] and *Aaron M. Milstone*[16]

[1] Division of Neonatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [3] Department of Anesthesia and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [4] Armstrong Institute for Patient Safety and Quality, Johns Hopkins Medicine, Baltimore, MD, United States, [5] Byramjee-Jeejeebhoy Government Medical College-Johns Hopkins University Clinical Research Site, Pune, India, [6] Department of Pediatrics, Byramjee-Jeejeebhoy Government Medical College, Pune, India, [7] Department of Neonatology, Bharati Vidyapeeth Deemed to Be University Medical College, Pune, India, [8] Department of Pediatrics, Bharati Vidyapeeth Deemed to Be University Medical College, Pune, India, [9] Department of Pediatrics, King Edward Memorial Hospital, Pune, India, [10] Department of Pediatrics, Dr. D. Y. Patil Medical College, Pune, India, [11] Department of Hospital Epidemiology and Infection Control, Johns Hopkins Hospital, Baltimore, MD, United States, [12] Division of Infectious Diseases, Department of Pediatrics, University of Pennsylvania, Philadelphia, PA, United States, [13] Centers for Disease Control and Prevention, Atlanta, GA, United States, [14] Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, United States, [15] Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [16] Division of Pediatric Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States

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Edited by:
Shi Yuan,
Children's Hospital of Chongqing Medical University, China

Reviewed by:
Tuuli Metsvaht,
University of Tartu, Estonia
Shan He,
The First People's Hospital of Yunnan Province, China

***Correspondence:**
Julia Johnson
jjohn245@jhmi.edu

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Objective: To implement the Comprehensive Unit-based Safety Program (CUSP) in four neonatal intensive care units (NICUs) in Pune, India, to improve infection prevention and control (IPC) practices.

Design: In this quasi-experimental study, we implemented CUSP in four NICUs in Pune, India, to improve IPC practices in three focus areas: hand hygiene, aseptic technique for invasive procedures, and medication and intravenous fluid preparation and administration. Sites received training in CUSP methodology, formed multidisciplinary teams, and selected interventions for each focus area. Process measures included fidelity to CUSP, hand hygiene compliance, and central line insertion checklist completion. Outcome measures included the rate of healthcare-associated bloodstream infection (HA-BSI), all-cause mortality, patient safety culture, and workload.

Results: A total of 144 healthcare workers and administrators completed CUSP training. All sites conducted at least 75% of monthly meetings. Hand hygiene compliance odds increased 6% per month [odds ratio (OR) 1.06 (95% CI 1.03–1.10)]. Providers completed insertion checklists for 68% of neonates with a central line; 83% of checklists were fully completed. All-cause mortality and HA-BSI rate did not change significantly after CUSP implementation. Patient safety culture domains with greatest improvement were management support for patient safety (+7.6%), teamwork within units (+5.3%), and organizational learning—continuous improvement (+4.7%). Overall workload increased from a mean score of 46.28 ± 16.97 at baseline to 65.07 ± 19.05 at follow-up ($p < 0.0001$).

Conclusion: CUSP implementation increased hand hygiene compliance, successful implementation of a central line insertion checklist, and improvements in safety culture in four Indian NICUs. This multimodal strategy is a promising framework for low- and middle-income country healthcare facilities to reduce HAI risk in neonates.

Keywords: neonate, healthcare-associated infection, patient safety, hand hygiene, aseptic technique, patient safety culture, multimodal strategy, bloodstream infection

INTRODUCTION

As facility-based births increase worldwide, low- and middle-income countries (LMIC) increasingly provide care for premature and sick neonates in neonatal intensive care units (NICUs) and special care nurseries (1). Hospitalized neonates are uniquely vulnerable to healthcare-associated infections (HAI) (2, 3). Poor infection prevention and control (IPC) practices augment this risk in many LMIC healthcare facilities (4). The burden of HAI in hospitalized neonates in LMICs exceeds that of facilities in high-income settings (5). The predominance of multi-drug resistant Gram-negative HAIs, which have limited treatment options and are associated with high morbidity and mortality in neonates, underscores the urgency of prevention interventions (6–8).

The World Health Organization (WHO) recommends implementation of multimodal improvement strategies for IPC with the following five elements: (1) system change, (2) training and education, (3) monitoring and feedback, (4) reminders and communication, and (5) culture change (9, 10). The Comprehensive Unit-based Safety Program (CUSP) is a multimodal improvement strategy that has been successfully implemented to improve IPC practices. CUSP has been used to reduce risk of central line-associated bloodstream infections (CLABSIs) and other HAIs in a variety of healthcare settings and populations (11–17). CUSP fosters the creation of a unit-based multidisciplinary team and empowers staff to assume responsibility for change, improving local patient safety culture and compliance with best practices to reduce HAIs and other threats to patient safety (18). While CUSP has been successfully applied internationally in high-income settings, including in Saudi Arabia and the United Arab Emirates, there is limited experience in NICU and LMIC settings (16, 17). Our objective was to assess the performance of CUSP in NICUs in an LMIC setting to guide IPC improvement strategies, reduce HAI risk in hospitalized neonates, and improve patient safety culture.

METHODS

In this quasi-experimental study, we implemented CUSP to improve adherence to evidence-based IPC practices in four tertiary care NICUs in Pune, India. Consent was obtained from all healthcare workers (HCWs) who completed surveys. This study was approved by the Johns Hopkins Medicine Institutional Review Board, the ethics committees of all participant sites, and the Indian Health Ministry's Screening Committee. This manuscript uses the SQUIRE 2.0 standards for reporting (19).

Study Sites

All participant sites are tertiary care facilities with high-volume NICUs located in Pune, India, though referral patterns and patient demographics differ. Byramjee Jeejeebhoy Government Medical College (BJGMC) is a government medical college affiliated with Sassoon Hospital, which has a 60-bed NICU. King Edward Memorial (KEM) Hospital is a non-governmental facility run by a charitable trust and has a 46-bed NICU. Dr. D. Y. Patil Medical College is a private medical college and has a 26-bed NICU. Bharati Vidyapeeth Deemed University Medical College is a private medical college and has a 60-bed NICU. All hospitals are delivery centers and admit both inborn and outborn neonates.

CUSP Implementation

CUSP is a validated strategy to empower staff to improve unit-level patient safety and consists of the following steps: (1) educate staff on the science of safety, (2) engage staff in identifying defects, (3) partner with a senior executive, (4) identify and learn from defects, and (5) implement teamwork tools (20). CUSP methodology has previously been described in the literature and the CUSP toolkit is publicly available on the Agency for Healthcare Research and Quality's (AHRQ) website at www.ahrq.gov (11, 20, 21). In this study, CUSP was used to improve HCW adherence to evidence-based IPC practices and reduce HAI risk in the NICU (see conceptual framework, **Figure 1**). Site staff received training in CUSP methodology and

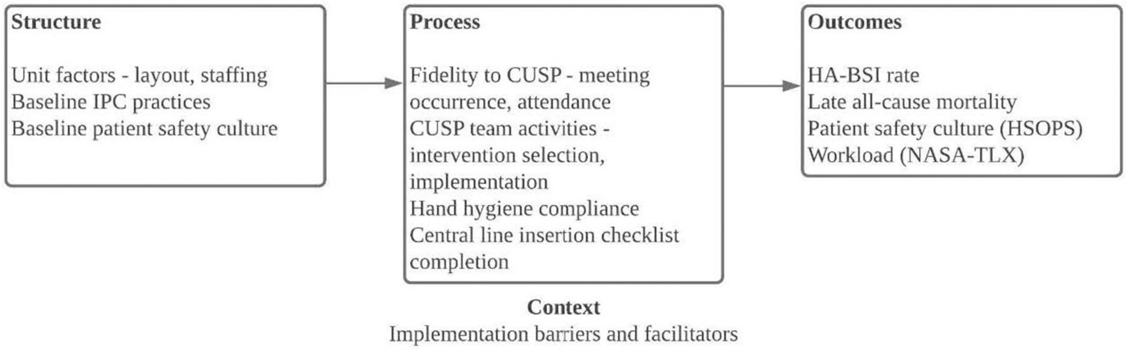

FIGURE 1 | Conceptual framework for CUSP implementation at four tertiary care neonatal intensive care units in Pune, India. CUSP, Comprehensive Unit-based Safety Program; HA-BSI, healthcare-associated bloodstream infections; HSOPS, Hospital Survey on Patient Safety Culture; IPC, infection prevention and control; NASA-TLX, National Aeronautics and Space Administration Task Load Index.

formed multidisciplinary teams led by a CUSP nurse champion and physician champion. Monthly CUSP meetings were attended by CUSP facilitators. Teams were additionally supported by monthly coaching calls.

Baseline IPC Assessments

Baseline IPC assessments of practices relevant to neonatal care at the facility level and within the Labor & Delivery ward and NICU were conducted in February 2017 and January 2018 using the Infection Control Assessment Tool (ICAT), 2nd version (2009) (22, 23). We supplemented the ICAT with questions specific to neonatal care, such as the storage and preparation of breast milk and formula feeds, umbilical catheter insertion and maintenance, and isolette and radiant warmer cleaning and disinfection. After review of these assessments and discussions with key local stakeholders, we identified three focus areas for CUSP: hand hygiene, aseptic technique for invasive procedures, and medication and intravenous (IV) fluid preparation and administration. For the third focus area, medication and IV fluid preparation and administration, sites were additionally provided an injection safety assessment tool that guided site self-assessment of existing practices (see **Supplementary Material**).

Selection and Implementation of Interventions

After CUSP teams were formed, unit-level staff selected interventions for the three focus areas, hand hygiene, aseptic technique for invasive procedures, and medication and IV fluid preparation and administration. For each pre-selected focus area, sites completed a two-question Staff Safety Assessment (SSA), adapted from the CUSP toolkit to each focus area in order to elicit staff perceptions of threats to patient safety within each focus area (**Supplementary Table 1**). After analyzing SSA responses, each CUSP team identified and implemented targeted interventions for each focus area. All sites initiated hand hygiene monitoring and implemented a central line insertion checklist (see **Supplementary Material**). Other interventions were selected and implemented at sites' discretion (**Table 1**). For focus area 2, creation of a central line maintenance audit tool was requested; completion of this tool was encouraged but not monitored (see **Supplementary Material**). For focus area 3, the injection safety assessment tool was used to support site assessments of existing practices and selected of interventions, which included use of multi-dose medication vials with a lower concentration, thereby reducing number of doses per vial, use of dedicated staff for preparation of all medications and IV fluids, and moving medication and IV fluid preparation to a separate space outside of the immediate patient care area (**Figure 1**). Notably, most medications administered in site NICUs are admixed in the patient care areas, rather than in the hospital's central pharmacy.

During monthly CUSP coaching calls, study team CUSP coaches and facilitators introduced adapted CUSP tools to support the implementation of interventions, such as the SSA and Patient Safety Rounds (see **Supplementary Material**) (21).

Outcomes

Process measures included CUSP training participation, monthly meeting occurrence and attendance, hand hygiene compliance, and central line insertion checklist completion. Outcome measures included the rate of healthcare-associated bloodstream infections (HA-BSI), all-cause mortality, patient safety culture, and workload.

Process Measures

CUSP Participation

We recorded attendance of all participants in CUSP training by name, role, and site. Each site recorded attendance of all participants by name and role at each monthly CUSP meeting.

Hand Hygiene Compliance

Hand hygiene compliance was measured by direct observation using trained external observers via the SpeedyAudit^{TM} application (HandyMetrics Corporation, Toronto, Canada). Hand hygiene compliance was recorded by HCW role and the five moments of hand hygiene: (1) before touching a patient; (2) before clean/aseptic procedures; (3) after body fluid exposure risk; (4) after touching a patient; and (5) after touching patient

TABLE 1 | CUSP interventions, general and by focus area, categorized by the five elements of the WHO multimodal IPC improvement strategy.

	System change	Training and education	Monitoring and feedback	Reminders and communication	Culture of safety
General	Creation of multidisciplinary CUSP team* Senior executive linked with unit* Infection control member of CUSP team* CUSP nurse to support interventions* Dedicated unit staff to decrease turnover	CUSP methodology training for administrators and unit-level staff* CUSP orientation for new unit staff Transition training for CUSP sustainability* HA-BSI root cause analysis training*	HA-BSI rate monitoring* Sharing of HA-BSI data at monthly CUSP meetings* Monitoring of CUSP meeting frequency, attendance, and participation*	Use of WhatsApp group to facilitate CUSP champion communication with study team* Use of WhatsApp groups to announce CUSP meetings, circulate agenda, and distribute information* Monthly CUSP coaching calls*	Creation of CUSP mission statement focused on patient safety* CUSP team logo design Display of mission and logo in unit Engagement of staff in identifying threats to safety via SSA*
Hand hygiene	Involvement of mothers and families in HH Change in HH product to reduce allergic dermatitis Assessment of supply chain issues Senior executive involvement in addressing supply chain issues Creation of additional ABHR storage space to avoid stock outage Emergency cart stocked with HH supplies	Group HH demonstration sessions Video-based HH education Targeted training for HH moments with poor compliance* Training for new interns by senior residents Training of mothers on HH technique Involvement of mothers in education of other mothers	Internal HH compliance monitoring using SpeedyAudit™ application* Sharing of HH data at monthly CUSP meetings* Feedback of HH data to unit staff* Individualized feedback for those with poor compliance CCTV use for targeted HH monitoring and feedback Appreciation of unit staff following best HH practices	Posters describing five moments of HH and importance of HH Bedside HH reminders Televised reminders in staff areas	HH SSA completion* HH focused mission statement* Emphasis on importance of HH by all unit staff* Coordination with other departments to motivate visiting staff to perform HH Participation in World Hand Hygiene Day*
Aseptic technique	Implementation of central line insertion checklist* Implementation of central line maintenance checklist*	Use of slide presentation and videos to train staff on aseptic technique* NABH care bundle training materials Training for new interns by senior residents	Monthly audits of central line insertion checklist completion* Sharing of checklist completion data at monthly CUSP meetings*	WhatsApp group reminders for CL insertion and maintenance checklist completion Use of WhatsApp groups to circulate training materials, posters, and NABH care bundle information	Aseptic technique SSA completion* Nurses/staff empowered to stop aseptic procedure if appropriate steps not followed*
Medication and IV fluids	Dedicated staff assigned to prepare all injections Dedicated injection preparation space outside of immediate patient care area Change in use of multi-dose vials with lower medication concentration when available Additional refrigerated storage for medications Change in standard injection times to reduce workload	Use of slide presentation to train staff on injection safety* Training for new interns by senior residents	Observation of hub cleaning practices Injection safety audit*	Posters detailing steps of medication preparation Bedside reminder flags for scrubbing the hub	Medication and intravenous fluid preparation and administration SSA completion*

*Interventions were selected and implemented by CUSP teams and site-specific. *Interventions implemented by all sites. ABHR, alcohol-based hand rub; CL, central line; CUSP, Comprehensive Unit-based Safety Program; HH, hand hygiene; IPC, infection prevention and control; IV, intravenous; NABH, National Accreditation Board of Hospitals and Healthcare Providers (India); SSA, Staff Safety Assessment; WHO, World Health Organization.*

TABLE 2 | CUSP team meeting frequency and attendance by site and month, June 2018-September 2019.

	Site 1	Site 2	Site 3	Site 4
Meetings took place, n (%)	16 (100)	15 (94)	12 (75)	12 (75)
Number of attendees, mean	11.7	14.8	8.8	12.1
Meetings attended by, n (%)				
Physician champion	16 (100)	15 (100)	11 (92)	12 (100)
Nurse champion	16 (100)	13 (87)	11 (92)	12 (100)
Senior nurse	14 (88)	5 (33)	0	8 (67)
Infection control	7 (44)	13 (87)	9 (75)	12 (100)
Senior executive	4 (25)	1 (7)	6 (50)	9 (75)
CUSP facilitator	16 (100)	15 (100)	11 (92)	11 (92)

Number of attendees (summary and by month) includes only meeting participants from the site, not the CUSP facilitator or any other study staff. CUSP facilitator attendance is noted separately. CUSP, Comprehensive Unit-based Safety Program.

surroundings (24). Hand hygiene data by HCW role and moment of hand hygiene were reported monthly and shared with site CUSP teams and unit staff throughout the study period.

Central Line Insertion Checklist Completion

The central line insertion checklist was adapted from the Johns Hopkins Hospital Pediatric Central Arterial and Venous Catheter Insertion Checklist with input from local stakeholders (see tools included in **Supplementary Material**). Sites implemented the central line insertion checklist in January-February 2019; none of the sites had a similar checklist in place prior to the study. Checklist completion was monitored by monthly audit completed by external assessors, with an assessment of central line checklist presence and completion in the medical record of neonates with a central line in place, and reported monthly at CUSP meetings.

Outcome Measures

Healthcare-Associated Bloodstream Infections and All-Cause Mortality

HA-BSI was defined as culture-confirmed BSI on hospital day 3 or greater. The monthly rate of HA-BSI was expressed as cases per 1,000 patient-days. Blood cultures were obtained at the discretion of the clinical teams and processed at site microbiology laboratories. For the primary outcome of HA-BSI, organisms deemed as likely contaminants (per categorization as a common commensal per the Centers for Disease Control and Prevention National Healthcare Safety Network) were excluded, with the exception of coagulase negative Staphylococcus (CONS), one of the most common HA-BSI pathogens in hospitalized neonates (2, 25). All-cause mortality was defined as the number of deaths per 100 admissions among neonates admitted for at least 3 days. HA-BSI and mortality data was collected as part of a concurrent prospective cohort study enrolling all neonates admitted to the NICU in which three sites participated (26). The fourth site reported unit-level HA-BSI and mortality data for outcome ascertainment.

Patient Safety Culture

Patient safety culture was assessed at baseline and follow-up using the Agency for Healthcare Research and Quality (AHRQ) Surveys on Patient Safety Culture (SOPS^{TM}) Hospital Survey (HSOPS) version 1.0 (27). The HSOPS consists of 42 items organized into 12 composite dimensions that assess elements of patient safety culture using a Likert response scale as well as nine items assessing respondent characteristics (**Supplementary Table 2**). The survey was administered in English, Marathi, or Hindi based on respondent preference. Survey responses were anonymous, and baseline and follow-up survey responses were not linked.

Workload

Workload was assessed at baseline and follow-up using the National Aeronautics and Space Administration Task Load Index (NASA-TLX) (28). The NASA-TLX assesses workload across six domains: mental demand, physical demand, temporal demand, effort, performance, and frustration. Each domain is assessed by a single item on a 20-point continuous scale. The NASA-TLX was administered with the HSOPS; responses were also anonymous and not linked.

Statistical Analysis

Logistic regression models were used to describe trends in hand hygiene compliance after CUSP implementation. The models included month and allowed for comparisons across site and by HCW role. All regression models accounted for potential autoregressive correlation of rates within a site over time; standard errors for the pooled analyses were estimated using robust variance estimates.

Descriptive analyses included summarizing baseline and post-implementation HA-BSI rates and all-cause mortality overall and by site. The site-specific baseline and post-implementation HA-BSI and mortality rates were compared using two-sample Poisson tests. The pooled relative monthly HA-BSI and mortality rates comparing the post-implementation and baseline periods were estimated using Poisson regression models with the number of HA-BSI or deaths as the outcome, main effect for the post-implementation and baseline periods and offset for total exposure time (patient-days or admissions).

For HSOPS analysis, percent positive scores (PPS) by item were calculated by dichotomizing responses and reverse coding scores for negative items. Mean PPS for composite domains were calculated by averaging PPS across items included in each domain. Comparison of baseline and follow-up patient safety culture was performed by site-level analysis of the difference in mean PPS for each composite domain. Confidence intervals (CIs) for the change in the mean PPS for composite domains were generated using a bootstrap procedure. Given that it was not possible to link responses for a respondent who participated in both baseline and follow-up surveys, the bootstrap procedure was used to replicate this potential clustering by resampling

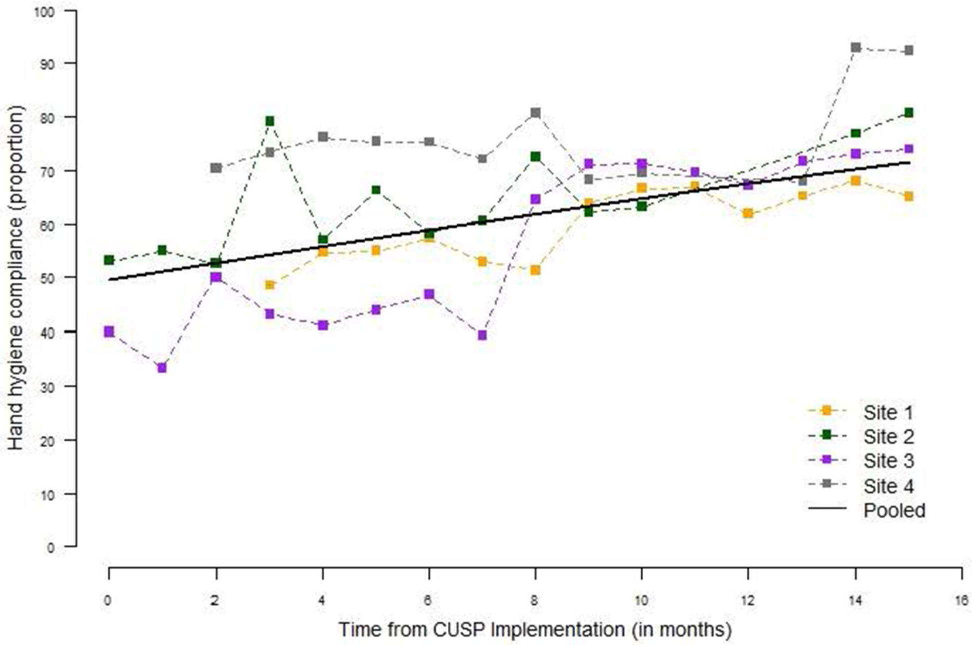

FIGURE 2 | Hand hygiene compliance by site and month, June 2018–September 2019. Monthly hand hygiene compliance was expressed as the proportion of monthly observations compliant, by site for all healthcare worker roles. Hand hygiene was monitored monthly via direct observation by trained observers. There were 8,684 opportunities for hand hygiene across all four sites over the course of the study period. The pooled hand hygiene compliance is based on a logistic regression model for observation compliance as a function of month from CUSP implementation.

respondents with replacement within site and pre- and post-intervention surveys. The reported bootstrap CIs are based on 1000 bootstrap samples and use the bias-corrected and accelerated method.

For NASA-TLX analysis, mean scores were calculated at baseline and follow-up for the six domains of workload. An overall workload score was calculated by summing the six domain scores at baseline and at follow-up, for a maximum score of 120. Baseline and post-intervention means were compared using Student's t-test. A p-value <0.05 was considered statistically significant.

All statistical analyses were completing using Stata version 15.0 (Stata Corp., College Station, TX) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Process Measures

CUSP Methodology Training

Across the four sites, 144 HCWs and administrators participated in CUSP methodology training in March 2018. Central training was attended mostly by administrators and senior leadership, as well as physician and nurse champions for each site. Site-based training included primarily unit-based staff as well as infection control staff. By the conclusion of training, all sites identified CUSP team members, including physician and nurse champions, a senior executive partner, infection control staff, and additional unit-based physicians and nurses.

CUSP Meetings and Coaching Calls

CUSP meetings took place monthly at each site over the course of the study period (**Table 2**). All sites conducted at least 75% of monthly meetings, with average attendance ranging from 8.8 to 14.8 participants per meeting across sites. The proportion of monthly meetings attended was highest among physician and nurse champions (87–100%). Senior executive attendance varied from 7% to 75%.

Hand Hygiene Compliance

There were 8684 hand hygiene observations across the sites over the course of the study period with all four sites collecting hand hygiene observations within 3 months of CUSP implementation (**Figure 2**). From the pooled analysis of all four sites, the proportion of compliant hand hygiene observations during the month of CUSP implementation was 51% (95% confidence interval (CI) 40-62%) and increased significantly to 56% (95% CI 46–65%), 65% (95% CI 57–72%), and 73% (95% CI 65–81%) by the 3rd, 9th and 15th month, respectively, following CUSP implementation; odds of hand hygiene compliance increased 6% per month, odds ratio (OR) 1.06, 95% CI 1.03–1.10). All sites had a statistically significant increase in the estimated hand hygiene compliance from CUSP implementation to the 15th month thereafter: site

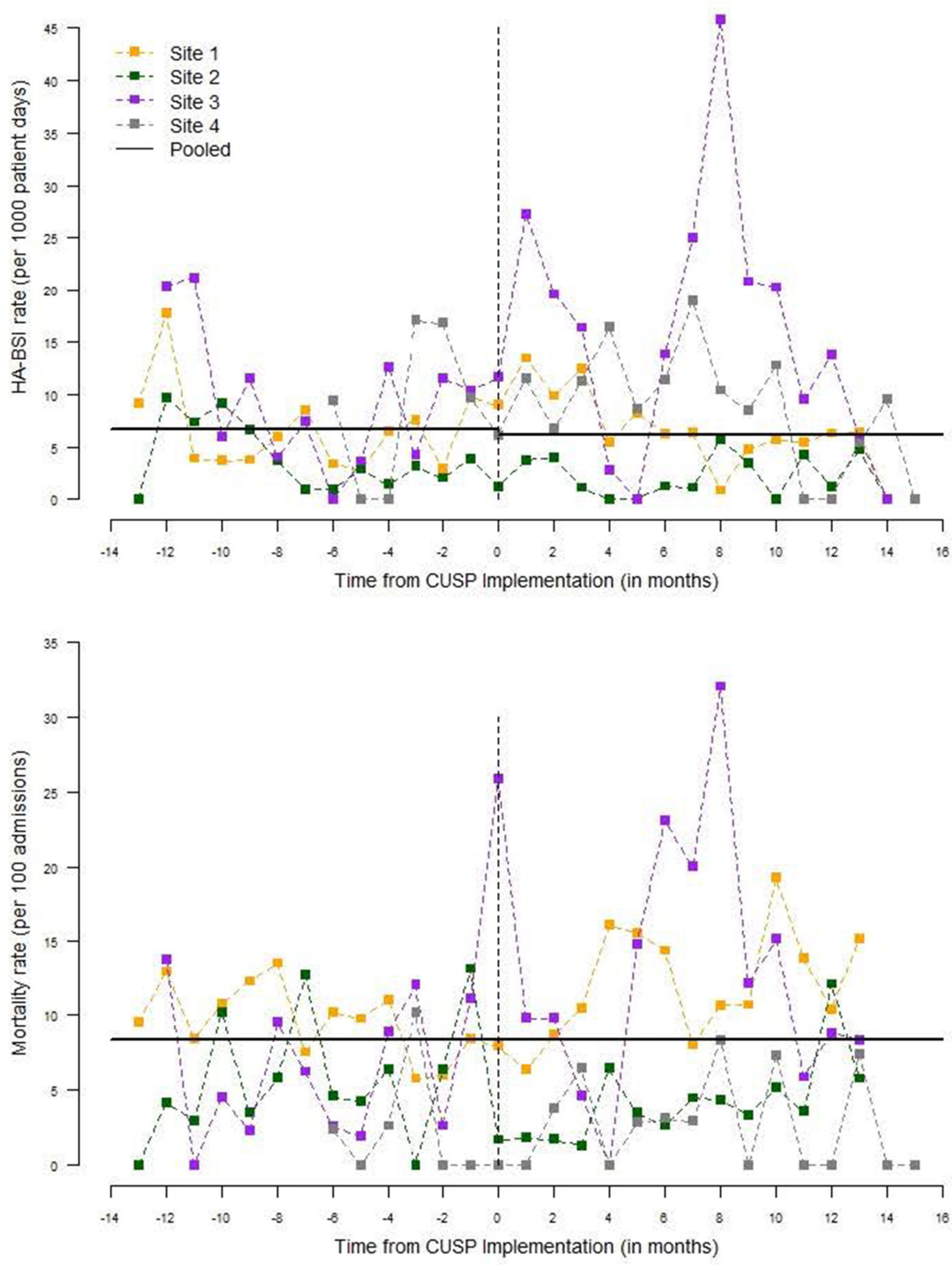

FIGURE 3 | Healthcare-associated bloodstream infection rate and all-cause mortality by site and month. The monthly HA-BSI was expressed as cases per 1,000 patient-days. All-cause mortality was expressed as deaths per 100 admissions among neonates admitted for at least 3 days. The pooled estimates are based on a Poisson regression model for the monthly rate of HA-BSI or mortality as a function of post- vs. pre-CUSP implementation. CUSP, Comprehensive Unit-based Safety Program; HA-BSI, healthcare-associated bloodstream infection.

1 from 48 to 67% (OR 1.05, 95% CI 1.04–1.07), site 2 from 52 to 78% (OR 1.08, 95% CI 1.06–1.11), site 3 from 33 to 76% (OR 1.13, 95% CI 1.10–1.16), and site 4 from 61 to 87% (OR 1.10, 95% CI 1.01–1.19). The rate of change of hand hygiene compliance over time did not differ by HCW role ($p = 0.988$).

Central Line Insertion Checklist Completion

From January 2019 until September 2019, there were 486 neonates who had a central line in place at time of monthly checklist audit. For site 1 ($n = 146$), 68% of neonates with a central line in place had an insertion checklist present in the medical record; site 2 ($n = 166$) 100%, site 3 ($n = 136$) 48%,

TABLE 3 | Healthcare-associated bloodstream infection rate and all-cause mortality at baseline and post-intervention, by site.

HA-BSI	HA-BSI cases	Patient-days	HA-BSI rate per 1,000 patient-days	RR (95% CI)
Site 1				
Baseline	114	17,743	6.4	Ref
Post-intervention	142	19,953	7.1	1.11 (0.87–1.42)
Site 2				
Baseline	47	11,452	4.1	Ref
Post-intervention	26	12,152	2.1	**0.52 (0.32–0.84)**
Site 3				
Baseline	28	3,133	8.9	Ref
Post-intervention	49	3,188	15.4	**1.72 (1.08–2.74)**
Site 4				
Baseline	13	1,369	9.50	Ref
Post-intervention	34	3,924	8.66	0.91 (0.48–1.73)
All-cause mortality	**Deaths**	**Admissions**	**Deaths per 100 admissions**	**RR (95% CI)**
Site 1				
Baseline	214	2,192	9.76	Ref
Post-intervention	220	1,850	11.89	1.21 (1.00–1.46)
Site 2				
Baseline	47	787	5.97	Ref
Post-intervention	35	839	4.17	0.68 (0.44–1.05)
Site 3				
Baseline	30	481	6.24	Ref
Post-intervention	61	488	12.50	**2.00 (1.29–3.10)**
Site 4				
Baseline	7	245	2.86	Ref
Post-intervention	15	552	2.72	0.95 (0.39–2.34)

Healthcare-associated bloodstream infections were defined as positive blood cultures with a known neonatal bacterial or fungal pathogen occurring on hospital day 3 or greater. Patient-days at risk were calculated as patient-days from hospital day 3 until NICU exit. All-cause mortality was defined as deaths per 100 admissions among neonates admitted for at least 3 days. CI, confidence interval; HA-BSI, healthcare-associated bloodstream infection; RR, relative rate. Bolded values reach statistical significance.

and site 4 ($n = 38$) 66%. Site 4's data were only representative of the last 5 months of checklist use; data were collected on checklist presence and completion, but not on the total number of neonates with central lines during the prior 4 months. Among checklists present in the chart ($n = 364$), 83% were completed (no required fields left blank).

Outcome Measures

Healthcare-Associated Bloodstream Infections

During the baseline period, there were 202 HA-BSI cases, with an HA-BSI rate of 5.99 per 1,000 patient-days (**Figure 3**). During the post-intervention period, there were 251 HA-BSI cases, with an HA-BSI rate of 6.40 per 1,000 patient-days. Overall, there was no statistically significant change in the monthly HA-BSI rate from baseline to the post-intervention period, with a relative rate (RR) of 0.97 [95% confidence interval (CI) 0.92–1.03] (**Figure 3**). HA-BSI rates demonstrated seasonality with increased rates over the monsoon period (June-September), which coincided with the start of the post-intervention period. There was no change in monthly HA-BSI rates for sites 1 and 4 (**Table 3**). Site 2 demonstrated a decrease in monthly HA-BSI rate from baseline to post-intervention (RR 0.52; 95% CI 0.32–0.84), whereas site 3 had an increased monthly HA-BSI rate post-intervention (RR 1.72; 95% CI 1.08–2.74).

All-Cause Mortality

Monthly all-cause mortality was unchanged from baseline to the post-intervention period across the four sites (RR 1.00, 95% CI 0.69–1.46) (**Figure 3**). Sites 1, 2, and 4 had no change in monthly all-cause mortality, whereas site 3 had an increase from baseline to post-intervention (RR 2.00; 95% CI 1.29–3.10) (**Table 3**).

Patient Safety Culture

Respondent Characteristics

The baseline HSOPS was completed by 182 respondents (response rate 85.8%). The follow-up HSOPS was completed by 212 respondents (response rate 99.1%) (**Table 4**). The majority of respondents were nurses, 163 (89.6%) at baseline and 182 (85.0%) at follow-up. All respondents identified as having direct patient contact.

Survey Results

High-scoring dimensions at baseline included teamwork within units (mean PPS 81.7% across all sites), supervisor/manager expectations and actions promoting patient safety (78.0%),

TABLE 4 | Hospital Survey on Patient Safety Culture respondents by healthcare worker role at baseline and follow-up, by site.

	Nurse $n = 345$	Physician $n = 47$	Other $n = 1$	Unknown $n = 3$	Total $n = 396$
Site 1					
Baseline	64	0	0	0	64
Follow-up	72	1	0	1	74
Site 2					
Baseline	53	1	0	0	54
Follow-up	58	6	1	2	67
Site 3					
Baseline	19	6	0	0	25
Follow-up	15	12	0	0	27
Site 4					
Baseline	27	12	0	0	39
Follow-up	37	9	0	0	46
Total					
Baseline	163	19	0	0	182
Follow-up	182	28	1	3	214

The HSOPS was completed anonymously by HCWs at baseline and follow-up. Respondents could select from multiple choice options of staff positions or provide a free text response. Categories of physicians (attending physician, resident physician, etc.) and nurses (charge/head nurse, nurse, nursing student, etc.) were collapsed. Only one respondent identified as an HCW other than physician or nurse. Three respondents did not provide their staff position. All respondents described themselves as having direct patient contact. No administrators completed the survey. HCW, healthcare worker; HSOPS, Hospital Survey on Patient Safety Culture.

organizational learning—continuous improvement (85.9%), and patient safety grade (81.8%). Improvements in mean PPS were seen in key dimensions of patient safety culture, with the largest increases in management support for patient safety (+7.6%), teamwork within units (+5.3%), management support for patient safety (+4.7%), and supervisor/manager expectations and actions promoting patient safety (+3.4%). Notably, there was a decrease in communication openness (−10.8%) and patient safety grade (−5.2%).

Survey responses varied by site (**Table 5**; **Supplementary Figures 1a–m**). For site 1, the largest gains were in frequency of event reporting (+30.3%), teamwork within units (+15.7%), teamwork across units (+11.9%), and management support for patient safety (+11.1%). For site 2, the composite domains with the greatest increases were non-punitive response to errors (+8.8%), organizational learning—continuous improvement (+8.4%), management support for patient safety (+6.6%), and staffing (+4.2%). For site 3, the largest gains were in supervisor/manager expectations & actions promoting patient safety (+11.7%), teamwork within units (+10.8%), non-punitive response to errors (+8.1%), and handoffs and transitions (+6.2%). For site 4, the greatest improvement was seen in management support for patient safety (+9.9%), patient safety grade (+4.9%), staffing (+3.8%), and organizational learning—continuous improvement (+2.8%).

In exploring overall trends, all four sites demonstrated improvements in the following composite domains: organizational learning—continuous improvement, management support for patient safety, and staffing. Communication openness was the only composite domain that had decreased follow-up scores at all sites.

Workload

Workload increased across all six domains from baseline to post-intervention periods (**Table 6**). Mental demand increased from a mean of 7.44 ± 4.35 to 11.16 ± 5.20 ($p < 0.0001$), physical demand from 7.57 ± 4.41 to 11.95 ± 4.85 ($p < 0.0001$), temporal demand from 7.55 ± 4.47 to 10.60 ± 4.25 ($p < 0.0001$), effort from 8.15 ± 4.06 to 11.10 ± 4.37 ($p < 0.0001$), performance from 10.07 ± 12.15 ($p < 0.0001$), and frustration from 5.50 ± 2.94 to 8.11 ± 4.45 ($p < 0.0001$). Overall workload increased from 46.28 ± 16.97 to 65.07 ± 19.05 ($p < 0.0001$).

DISCUSSION

Our study fostered the creation of multidisciplinary CUSP teams that collaboratively selected and implemented interventions to improve IPC practices in three focus areas, hand hygiene, aseptic technique for invasive procedures, and medication and IV fluid preparation and administration. CUSP enabled sites to pursue multimodal IPC improvement strategies that included a focus on patient safety culture, as championed by the WHO (29). This intervention led to an increase in hand hygiene but did not reduce HA-BSI or all-cause mortality during the study period. While one site did have a reduction in HA-BSI rate, another site experienced an increase in both HA-BSI and mortality, which was largely driven by an outbreak that occurred during the post-intervention period. The CUSP team was instrumental in developing an outbreak response and focusing on appropriate IPC interventions, including a heightened focus on the importance of hand hygiene.

CUSP did lead to process improvements known to reduce infection risk, including a marked improvement in hand hygiene and successful implementation of a central line insertion checklist. The success of CUSP implementation can also be measured by the observed culture change and practice changes. Over the course of the study period, it was evident that nurses became empowered to speak up in front of leadership and advocate for patient safety and nurses attending CUSP meetings increasingly felt ownership and pride in the interventions they were leading. Furthermore, monthly coaching calls facilitated sharing of strategies and dissemination of interventions among sites, serving as a new forum for collaboration among NICUs facing similar challenges.

All sites demonstrated improved hand hygiene over the course of the study period. Implementing a program of hand hygiene compliance monitoring along with feedback of data to CUSP teams and unit staff, constituted a powerful intervention. While all sites previously employed some form of hand hygiene compliance monitoring by infection control, there was no consistent feedback or sharing of data with unit-level staff prior to CUSP implementation. Monthly hand hygiene data provided direct feedback to CUSP teams regarding the impact of their interventions and provided an opportunity to tailor interventions to specific HCW roles and moments

TABLE 5 | Mean percent positive scores by composite dimension, baseline and follow-up Hospital Survey on Patient Safety Culture by site.

	Baseline (%)	Follow-up (%)	Difference (%)	95% CI (%)
Site 1 Teamwork within units	58.6	74.3	**+15.7**	**(5.9, 25.7)**
Supervisor/manager expectations and actions promoting patient safety	77.6	82.1	+4.5	(−4.2, 13.6)
Organizational learning—continuous improvement	91.1	92.2	+1.1	(−4.7, 6.8)
Management support for patient safety	55.6	66.7	**+11.1**	**(9.4, 21.2)**
Perceptions of patient safety	58.6	56.1	−2.5	(−10.7, 4.9)
Feedback and communication about error	57.3	64.0	+6.7	(−2.8, 17.2)
Communication openness	74.7	62.2	−12.5	(−21.9, −2.8)
Frequency of event reporting	32.3	62.6	**+30.3**	**(16.9, 43.3)**
Teamwork across units	53.0	64.9	**+11.9**	**(1.8, 22.2)**
Staffing	23.8	27.7	+3.9	(−1.5, 9.0)
Handoffs and transitions	53.4	54.8	+1.4	(−8.8, 11.9)
Non-punitive response to errors	28.1	28.4	+0.3	(−9.4, 10.8)
Patient safety grade	70.3	67.6	−2.7	(−17.7, 13.4)
Site 2 Teamwork within units	95.4	92.2	−3.2	(−7.5, 1.4)
Supervisor/manager expectations and actions promoting patient safety	85.6	86.6	+1.0	(−6.5, 8.1)
Organizational learning—continuous improvement	81.5	89.9	+8.4	(−0.1, 16.2)
Management support for patient safety	75.3	81.9	+6.6	(−2.7, 16.4)
Perceptions of patient safety	60.7	57.5	−3.2	(−10.7, 4.5)
Feedback and communication about error	73.8	73.1	−0.7	(−11.3, 9.5)
Communication openness	79.0	73.9	−5.1	(−13.9, 4.1)
Frequency of event reporting	66.7	64.2	−2.5	(−15.2, 10.1)
Teamwork across units	78.1	81.7	+3.6	(−4.2, 11.7)
Staffing	38.4	42.6	+4.2	(−2.1, 10.6)
Handoffs and transitions	68.1	62.1	−6.0	(−17.4, 5.6)
Non-punitive response to errors	39.5	48.3	+8.8	(−0.9, 17.8)
Patient safety grade	92.6	94.0	+1.4	(−7.1, 10.3)
Site 3 Teamwork within units	80.0	90.8	+10.8	(−2.8, 25.2)
Supervisor/manager expectations and actions promoting patient safety	67.0	78.7	+11.7	(−3.0, 26.6)
Organizational learning—continuous improvement	81.3	87.7	+6.4	(−5.5, 18.6)
Management support for patient safety	61.3	64.2	+1.9	(−12.8, 18.1)
Perceptions of patient safety	49.0	54.7	+5.7	(−7.2, 17.0)
Feedback and communication about error	56.0	42.5	−13.5	(−32.6, 6.3)
Communication openness	58.7	45.7	−13.0	(−32.9, 8.0)
Frequency of event reporting	52.0	34.6	−17.4	(−36.6, 2.5)
Teamwork across units	67.0	53.7	−13.3	(−26.0, 7.4)
Staffing	29.0	32.0	+3.0	(−5.5, 10.7)
Handoffs and transitions	52.8	59.0	+6.2	(−10.6, 24.0)
Non-punitive response to errors	40.0	48.1	+8.1	(−9.5, 27.1)
Patient safety grade	80.0	55.6	−24.4	(−47.9, 1.8)
Site 4 Teamwork within units	92.9	90.8	−2.1	(−8.7, 5.2)
Supervisor/manager expectations and actions promoting patient safety	81.9	78.2	−3.7	(−14.2, 7.0)
Organizational learning—continuous improvement	89.8	92.6	+2.8	(−4.3, 10.9)
Management support for patient safety	71.2	81.1	+9.9	(−1.6, 19.7)
Perceptions of patient safety	66.1	67.2	+1.1	(−8.0, 9.8)
Feedback and communication about error	67.2	60.3	−6.9	(−20.2, 6.3)
Communication openness	66.6	54.3	−12.3	(−26.0, 2.6)
Frequency of event reporting	57.8	55.8	−2.0	(−19.6, 14.3)
Teamwork across units	77.5	77.7	+0.2	(−9.4, 9.5)

(Continued)

TABLE 5 | Continued

	Baseline (%)	Follow-up (%)	Difference (%)	95% CI (%)
Staffing	28.8	32.6	+3.8	(−5.7, 12.7)
Handoffs and transitions	68.9	64.7	−4.2	(−19.1, 9.9)
Non-punitive response to errors	46.1	38.0	−8.1	(−23.1, 7.3)
Patient safety grade	84.2	89.1	+4.9	(−9.0, 19.8)

The HSOPS consists of 42 items into 12 composite domains that assess elements of patient safety culture using a Likert response scale. PPS by item were calculated by dichotomizing responses and reverse coding for negative items. Mean PPS for composite domains were calculated by averaging PPS across items included in each domain. Patient safety grade was determined by calculating mean response to a single item. HSOPS, Hospital Survey on Patient Safety Culture; PPS, percent positive score. Bolded values reach statistical significance.

of hand hygiene as needed. At the end of the study, sites committed to continue hand hygiene compliance monitoring and feedback of data.

Implementation of a central line insertion checklist are evidence-based practices that represented a paradigm shift in patient safety for these NICUs (30, 31). Prior to CUSP, none of the participant NICUs used pre-operative or pre-procedural checklists. Sites readily adapted its use into daily medical practice, with gradual increases in appropriate completion of checklists used. With checklist implementation, the importance of having an observer or assistant present for central line insertion was highlighted, which can be challenging in a resource-limited setting. The checklist also empowered nurses or other HCWs serving in the observer/assistant role to intervene if steps of appropriate aseptic technique were not followed. By site request, a central line maintenance audit tool was created by the study team, though its completion was not audited by study staff. Both the insertion checklist and the maintenance audit tool fit well into the existing healthcare system at our four sites, with checklists used for a variety of other indications.

During our baseline IPC assessments, we noted opportunities for improvement at all sites for practices related to medication and IV fluid preparation and administration. In a resource-limited setting, challenges to injection safety include reliance on multi-dose vials, reuse of single-dose vials, and large stock bottles of IV fluid solutions and topical antiseptics including alcohol and betadine, as well as preparation of medications and IV fluids within the immediate patient care area (32, 33). While it was not possible to transition to exclusive use of single-dose vials and eliminate use of large stock bottles, CUSP teams focused on how to improve injection safety by including IPC considerations in adapting existing workflow.

Multiple studies have demonstrated that improving patient safety culture across HSOPS domains is associated with lower HAI rates (34, 35). Sites demonstrated gains in key HSOPS domains of patient safety, including teamwork within units, supervisor/manager expectations and actions promoting patient safety, organizational learning—continuous improvement, and management support for patient safety. In considering the elements of the CUSP intervention, these are the domains in which one would expect improvement. Most gains did not reach statistical significance which likely reflects a relatively fixed sample size of HCWs employed within each unit. Our response rates for both baseline and follow-up surveys were excellent and we hope to explore whether these trends continue and assess generalizability of our findings by recruiting more sites.

We did not expect to improve other domains, such as staffing and teamwork across units, which were outside of the scope of our intervention. The notable decrease in communication openness across all sites should be explored further and addressed in moving CUSP forward. We did not see a significant improvement in patient safety grade, which consists of a single item asking respondents to assign a letter grade to their unit's patient safety. It is not surprising that respondents are more critical of patient safety after an intervention that raises knowledge and awareness of IPC practices and their impact on patient safety.

As measured by NASA-TLX across six domains, workload increased from baseline to the post-intervention period. To our knowledge, NASA-TLX assessment of workload has not previously been used in the context of CUSP implementation. Tubbs-Cooley et al. previously measured overall workload among neonatal, pediatric, and adult intensive care nurses using NASA-TLX; among NICU nurses who participated in this multi-center cross-sectional study, the mean overall workload was similar to that reported on our study, roughly midway between our baseline and post-intervention scores (36). CUSP implementation required a comprehensive unit-level shift in the approach to IPC and patient safety. While CUSP activities were led by the physician and nurse champions in conjunction with the CUSP team, selected interventions within the three focus areas required participation and commitment by all unit staff, especially those providing direct patient care. CUSP may have contributed to the increase in workload seen over the course of this study, though other unmeasured factors such as staffing changes or more complex patient load could have also contributed. Effect of CUSP activities on perceived workload should be monitored closely, given the association of increased NASA-TLX scores with HCW burnout (37). Furthermore, a single-center study in a United States NICU described an association between increased nursing workload with missed nursing care (38). CUSP should prioritize interventions that lighten workload by making work more efficient and less burdensome, though advocating for improved staffing may also be a critical CUSP activity.

Our intervention coincided with an increased focus on patient safety by the Indian Ministry of Health. Multiple sites

TABLE 6 | Workload among neonatal intensive care unit staff at baseline and post-intervention, as measured by NASA-TLX.

Item	Baseline, mean ± SD (range)	Post-intervention, mean ± SD (range)	*P*-value
Site 1			
Mental	8.78 ± 4.89	12.2 ± 4.73	**0.0001**
Physical	9.54 ± 4.87	13.06 ± 4.97	**<0.0001**
Temporal	8.89 ± 4.42	11.23 ± 4.09	**0.0016**
Effort	9.75 ± 4.66	11.81 ± 3.97	**0.0059**
Performance	10.60 ± 4.17	11.00 ± 4.60	0.5952
Frustration	6.27 ± 3.28	8.91 ± 4.32	**0.0001**
Overall	53.82 ± 16.67	68.21 ± 18.89	**<0.0001**
Site 2			
Mental	6.60 ± 4.18	9.65 ± 5.14	**0.0006**
Physical	6.41 ± 3.90	9.91 ± 4.62	**<0.0001**
Temporal	8.61 ± 4.54	8.69 ± 3.59	0.9189
Effort	7.00 ± 3.45	8.97 ± 3.64	**0.0030**
Performance	8.97 ± 4.95	12.73 ± 4.36	**<0.0001**
Frustration	5.35 ± 2.74	6.79 ± 3.69	**0.0186**
Overall	42.95 ± 16.79	56.74 ± 16.21	**<0.0001**
Site 3			
Mental	7.19 ± 4.10	14.61 ± 4.57	**<0.0001**
Physical	6.48 ± 3.54	15.30 ± 3.66	**<0.0001**
Temporal	5.93 ± 3.01	14.11 ± 4.07	**<0.0001**
Effort	7.92 ± 3.15	15.51 ± 4.35	**<0.0001**
Performance	10.72 ± 4.28	9.44 ± 6.27	0.3991
Frustration	5.48 ± 2.45	12.37 ± 5.35	**<0.0001**
Overall	43.72 ± 15.22	81.34 ± 15.66	**<0.0001**
Site 4			
Mental	6.57 ± 3.30	9.66 ± 5.12	**0.0018**
Physical	6.67 ± 3.74	11.17 ± 4.09	**<0.0001**
Temporal	4.91 ± 3.85	10.32 ± 4.03	**<0.0001**
Effort	7.26 ± 3.57	10.47 ± 3.83	**0.0002**
Performance	10.31 ± 4.06	14.76 ± 3.93	**<0.0001**
Frustration	4.46 ± 2.62	6.24 ± 2.97	**0.0048**
Overall	40.18 ± 14.74	62.61 ± 18.11	**<0.0001**
All sites			
Mental	7.44 ± 4.35	11.16 ± 5.20	**<0.0001**
Physical	7.57 ± 4.41	11.95 ± 4.85	**<0.0001**
Temporal	7.55 ± 4.47	10.60 ± 4.25	**<0.0001**
Effort	8.15 ± 4.06	11.10 ± 4.37	**<0.0001**
Performance	10.07 ± 4.43	12.15 ± 4.91	**<0.0001**
Frustration	5.50 ± 2.94	8.11 ± 4.45	**<0.0001**
Overall	46.28 ± 16.97	65.07 ± 19.05	**<0.0001**

The NASA-TLX was completed at baseline and post-intervention to assess workload across six domains on a 20-point continuous scale. Overall workload was calculated by summing scores for the six domains at baseline and post-intervention. NASA-TLX, National Aeronautics and Space Administration Task Load Index. Bolded values reach statistical significance.

underwent accreditation or government official visits during the study period. Our intervention aligned well with this mission, especially with regard to monitoring of hand hygiene compliance and use of a central line insertion checklist. Senior executive support of CUSP-driven interventions led to spread beyond the NICU, with adaptation of some interventions throughout the hospital.

Strengths of this study include use of a multidisciplinary team that worked together in an iterative process that allows for learning and is firmly grounded in creation of local patient safety culture to reduce HAI risk. This study demonstrated the ready adaptation of an existing toolkit that has proven success to a resource-limited setting. The selected focus areas included high-yield IPC practices, optimization of which has been linked to reduction of HA-BSI in a variety of healthcare settings. Site-driven selection of interventions, rather than a prepackaged IPC bundle, yielded locally appropriate solutions to IPC gaps that are more likely to be sustainable than financially burdensome interventions.

Limitations of this study include its duration and small sample size. A 16-month study period limited our capacity to assess the impact of the intervention on HA-BSI rates and mortality, especially given seasonality of infections in this setting, with higher rates seen during monsoon season. Additionally, the final focus area, medication and IV fluid preparation and administration, was introduced only 3 months prior to study end, limiting our capacity to assess the impact of selected interventions on outcomes of interest. However, improved hand hygiene and gains seen in patient safety culture are promising measures of success of this intervention. Though the advent of the coronavirus disease 2019 pandemic disrupted CUSP activities, sites have committed to sustaining the CUSP intervention. We intend to complete a follow-up assessment of the impact of CUSP, which will provide important information about CUSP sustainability in this setting.

CUSP is a promising multimodal strategy for healthcare facilities in resource-limited settings that encompasses key aspects of the WHO's IPC improvement strategy, including culture of safety. Our study outlines an approach to CUSP that can be readily adapted to NICUs in an LMIC setting and is feasible. Next steps include assessment of sustainability and generalizability of our findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins Medicine Institutional Review Board, Byramjee-Jeejeebhoy Government Medical College Ethics Committee, Dr. D. Y. Patil Medical College Ethics Committee, King Edward Memorial Hospital Ethics Committee, Bharati Vidyapeeth Medical College Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BR and AKa supported data collection. JJ and EC analyzed the data. JJ drafted the initial manuscript. All authors conceptualized and designed the study and contributed to the manuscript revision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.794637/full#supplementary-material

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BRIEF RESEARCH REPORT
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Inadequate Bioavailability of Intramuscular Epinephrine in a Neonatal Asphyxia Model

Sara K. Berkelhamer[1], Payam Vali[2], Jayasree Nair[3], Sylvia Gugino[3], Justin Helman[3], Carmon Koenigsknecht[3], Lori Nielsen[3] and Satyan Lakshminrusimha[2]*

[1] Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA, United States, [2] Department of Pediatrics, University California Davis School of Medicine, Sacramento, CA, United States, [3] Department of Pediatrics, University at Buffalo SUNY, Buffalo, NY, United States

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University of Alberta, Canada

***Correspondence:**
Sara K. Berkelhamer
berkelsa@uw.edu

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Background: Over half a million newborn deaths are attributed to intrapartum related events annually, the majority of which occur in low resource settings. While progress has been made in reducing the burden of asphyxia, novel approaches may need to be considered to further decrease rates of newborn mortality. Administration of intravenous, intraosseous or endotracheal epinephrine is recommended by the Newborn Resuscitation Program (NRP) with sustained bradycardia at birth. However, delivery by these routes requires both advanced skills and specialized equipment. Intramuscular (IM) epinephrine may represent a simple, low cost and highly accessible alternative for consideration in the care of infants compromised at birth. At present, the bioavailability of IM epinephrine in asphyxia remains unclear.

Methods: Four term fetal lambs were delivered by cesarean section and asphyxiated by umbilical cord occlusion with resuscitation after 5 min of asystole. IM epinephrine (0.1 mg/kg) was administered intradeltoid after 1 min of positive pressure ventilation with 30 s of chest compressions. Serial blood samples were obtained for determination of plasma epinephrine concentrations by ELISA.

Results: Epinephrine concentrations failed to increase following administration *via* IM injection. Delayed absorption was observed after return of spontaneous circulation (ROSC) in half of the studies.

Conclusions: Inadequate absorption of epinephrine occurs with IM administration during asphyxial cardiac arrest, implying this route would be ineffective in infants who are severely compromised at birth. Late absorption following ROSC raises concerns for risks of side effects. However, the bioavailability and efficacy of intramuscular epinephrine in less profound asphyxia may warrant further evaluation.

Keywords: resuscitation, epinephrine, intramuscular, asphyxia, neonatal, low-resource

INTRODUCTION

Despite advances in the delivery of both maternal and newborn care, an estimated 2.4 million infants do not survive their first month of life (1). Nearly ¼ of neonatal deaths can be attributed to intrapartum events or asphyxia, resulting in an estimated 0.58 million deaths annually (2). Beyond mortality are concerns for long term morbidity associated with intrapartum events. The World Health Organization estimates that between 4 and 9 million newborns are impacted by asphyxia annually with risks of long term developmental delays associated with physiologic compromise at birth (3, 4). These data may even underestimate the incidence with the challenges of identifying cases in under resourced areas (5, 6). The burden of disease falls greatest on low and middle income countries where the majority of early newborn deaths occur (5).

While reduction in morbidity and mortality associated with birth asphyxia requires improvement in all levels of perinatal care, improved resuscitation and stabilization of asphyxiated infants could impact millions of infants worldwide. Resuscitation efforts at birth play a critical role in determining outcomes, influencing both risk of mortality and incidence of neurodevelopmental disability (4, 7, 8). Access to training and materials to provide simple resuscitative care (through programs including *Helping Babies Breathe*) has been shown to improve outcomes in low resource settings with reduction of early mortality and stillbirth rates (9). Despite these advances, outcomes following intrapartum related events remain a concern. Notably, the annual rate of reduction for neonatal mortality lags significantly behind rates of reduction for maternal and under 5 child mortality (10, 11). Additional simple measures to improve the care of infants compromised at birth may be needed to further reduce the burden.

The Newborn Resuscitation Program (NRP) utilizes recommendations provided by the International Liaison Committee on Resuscitation (ILCOR) to define an algorithm for care of compromised newborns. This program is currently used in over 130 countries worldwide and influences the care of millions of infants at delivery. These guidelines recommend administration of epinephrine by umbilical venous catheter (UVC), intraosseous (IO) needle, or endotracheal tube (ETT) with sustained bradycardia despite effective ventilation and chest compressions (12). However, these routes of administration require advanced skills, specialized equipment and take several minutes to secure even in well-resourced settings where training and equipment are readily available (13, 14). Simplified algorithms, including *Helping Babies Breathe*, provide guidance for basic resuscitative care. However, intramuscular (IM) epinephrine could be administered with limited training, use of commonly accessible resources and with limited interruption of resuscitative efforts. As every minute delay potentially impacts outcomes with asphyxia (15), a simple, efficient mode of epinephrine delivery has potential application in the context of both HBB or NRP when access cannot be obtained.

While epinephrine has inotropic, lusitropic, and chronotropic actions, its vasoconstrictor properties mediated by α-adrenergic receptors are primarily responsible for its effectiveness in CPR (16). Administration of epinephrine is believed to induce intense peripheral vasoconstriction resulting in elevated systemic vascular resistance and an increase in coronary perfusion pressure to improve coronary flow (17). IM epinephrine has known clinical efficacy and is widely used in the treatment of anaphylaxis, suggesting this route of delivery might also be considered with resuscitation. The ease of administration makes this approach a practical and efficient option for providers at all levels, an important consideration in less resourced environments where attendants skilled in intubation or line placement may not be available. While studies in a pediatric swine model suggest IM epinephrine may promote return of spontaneous circulation (ROSC) after cardiac arrest (18), the absorption and pharmacokinetics associated with this route of administration in the context of asphyxia remain unknown. Using a well-established ovine model of neonatal asphyxial arrest, we sought to determine bioavailability and pharmacokinetics associated with administration of IM epinephrine.

MATERIALS AND METHODS

Animal Studies

Four term gestation lambs (141–142 days) were used for this case series. Our protocol was performed on extra, unassigned lambs with a specific interest in comparing an alternative route of epinephrine administration to our prior studies evaluating bioavailability and pharmacokinetics with delivery *via* IO needle, UVC, or ETT (19, 20). ARRIVE guidelines were followed as possible, however our cohort was limited to 4 lambs and was not randomized or registered as a preclinical trial.

All animal work was approved by the Institutional Animal Care and Use Committee at the State University of New York at Buffalo (Protocol #PED10085N, approved 5.10.2018). Time dated term (140–141 day gestation) pregnant ewes were obtained from Newlife Pastures (Varysburg, New York, USA). Following an overnight fast, the ewes were anesthetized with intravenous diazepam and ketamine, intubated with a 10.0-mm cuffed ETT and ventilated with 21% oxygen and 2–3% isoflurane at 16 breaths/min. Ewes were continuously monitored with pulse oximetry and an end tidal CO_2 monitor. Cesarean section was performed on the anesthetized ewe with partial exteriorization of fetal lambs. Lambs were intubated and excess fetal lung fluid in the ETT was drained by gravity to simulate loss of lung liquid with labor. Thereafter, the ETT was occluded to prevent gas exchange during gasping in the asphyxia period. Fetal lambs were instrumented as described previously (21–23), with heparinized catheters placed into the right carotid artery and jugular vein for blood pressure measurements, blood draws to measure plasma epinephrine concentrations and preductal arterial blood gases. A 2-mm flow probe (Transonic Systems Inc., Ithaca, NY) was placed around the left carotid artery. A left thoracotomy was performed and a 4-mm flow probe was placed around the left pulmonary artery. The thoracotomy was closed in layers. ECG leads were attached at the right axilla, left axilla, and right inguinal area (3-lead EKG). The ECG100C (Biopac Systems, Inc.) was used with Acknowledge Software to record tracings of leads I, II, and III. Preductal arterial oxyhemoglobin saturation was monitored with a pulse oximeter placed on the right forelimb of the lamb (Masimo, Irvine, CA). Following instrumentation, a "baseline" blood gas and sample for epinephrine concentration was obtained. The umbilical cord was subsequently occluded and cut, and the lambs were moved from the maternal abdomen to the radiant warmer. During the asphyxia period, an umbilical arterial catheter was inserted to measure continuous invasive blood pressures. A low umbilical venous catheter was inserted 2 cm below the skin (and secured after confirming blood drawing back into the catheter).

Experimental Protocol

A 5-min period of asystole was observed prior to initiating resuscitation. Asystole was defined by the absence of carotid blood flow, arterial blood pressure, and heart rate (by auscultation). Resuscitation began by removing the ETT occluder and providing positive pressure ventilation (PPV) with 21% oxygen by means of a T-piece resuscitator at pressures of 35/5 cm H_2O (to delivery standard volumes and ventilation) at a rate of 40 breaths/min (24). Following 30s of ventilation, chest compressions at a compression-to-ventilation ratio of 3:1 were commenced with a simultaneous increase in inspired oxygen to 100%. Intramuscular epinephrine was administered into the deltoid muscle at 1 min from onset of resuscitation. A high dose of 0.1 mg/kg (1:1,000 concentration, 1 mg/mL) was utilized as we assumed there would be challenges with absorption and wanted to parallel prior published studies evaluating this route in an arrest model (18). Only a single dose was administered to simplify evaluation of pharmacokinetics. Synchronized chest compressions and PPV were continued until ROSC was achieved, defined as a sustained, perfusing rhythm with heart rate above 100 beats per minute.

An "arrest" arterial blood sample was obtained following 5 min of asystole but prior to initiation of resuscitation (time 0 of resuscitation). Thereafter, serial blood sampling was performed at minute 1–5, 7, 9, and 15 for blood gas analysis and epinephrine levels. The 1-min sample was drawn immediately prior to injection of epinephrine (**Figure 1**). Arterial blood samples were analyzed using a radiometer blood gas analyzer (ABL 800 FLEX, Denmark). Plasma epinephrine concentrations were analyzed by ELISA (Eagle Biosciences, Nashua, NY) with a limit of detection as defined by the assay of <0.005 ng/mL.

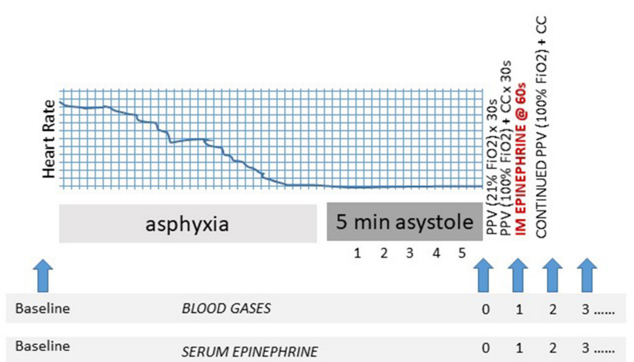

FIGURE 1 | Experimental design. Schematic identifying resuscitation protocol and blood sampling (blue arrows). CC, to chest compression; FiO_2, fraction of inspired oxygen; PPV, positive pressure ventilation; s, second.

Statistical Analysis

Continuous variables were analyzed by ANOVA with Tukey's *post-hoc* analysis. GraphPad Prism (San Diego, CA) was used for statistical analysis with significance defined as $p < 0.05$.

RESULTS

Demographics and Asphyxia

Four lambs were studied, including one singleton female, one singleton male, one twin female and one twin male with an average weight of 3.6 ± 0.9 kg. Baseline blood gases were comparable to those of prior experimental lambs with the blood gas at arrest demonstrating severe metabolic acidosis, hypercapnea, and elevated lactate levels (**Table 1**) (22). Time to asystole was a median (range) of 12.6 (8–15.5) min, also consistent with prior publications in the model (22).

Plasma Epinephrine Concentrations

Plasma epinephrine concentrations were evaluated at baseline (prior to asphyxia), arrest (0 min) and serially during resuscitation. There was no significant increase in plasma concentrations prior to ROSC with IM epinephrine administration (**Figure 2**). Increased concentrations were observed in 2 animals several minutes after ROSC (**Supplementary Table 1**). While epinephrine concentrations did not increase significantly following IM administration (**Figure 3**), delayed absorption occurred.

TABLE 1 | Blood gases at baseline and arrest.

		Blood gas at baseline			Blood gas at arrest		
Route	***N***	**pH**	**CO2**	**Lactate**	**pH**	**CO2**	**Lactate**
IM	4	7.19 ± 0.08	66 ± 12	3.3 ± 0.6	6.81 ± 0.08	126 ± 30	12.5 ± 4.4
*UVC**	11	7.10 ± 0.09	67 ± 7	4.9 ± 3.6	6.80 ± 0.09	146 ± 25	14.6 ± 6.7
*ETT**	11	7.16 ± 0.14	68 ± 7	4.8 ± 3.5	6.85 ± 0.04	132 ± 17	14.8 ± 5.1

Baseline samples were obtained following instrumentation but prior to asphyxia. Arrest samples were obtained after 5 min of asphyxia. [*]Experimental data from Vali et al. (22). N represents the number of lambs, Data are mean ± SD. IM, intramuscular; UVC, umbilical venous catheter; ETT, endotracheal tube.

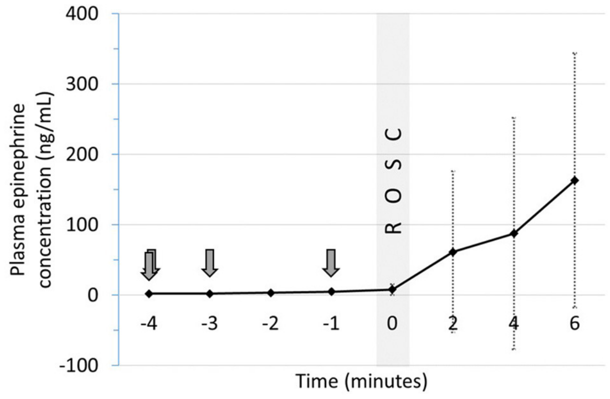

FIGURE 2 | Plasma epinephrine concentrations following IM epinephrine in relation ROSC. Arrows indicate time of epinephrine administration. Data are mean ± SEM. ROSC, return of spontaneous circulation.

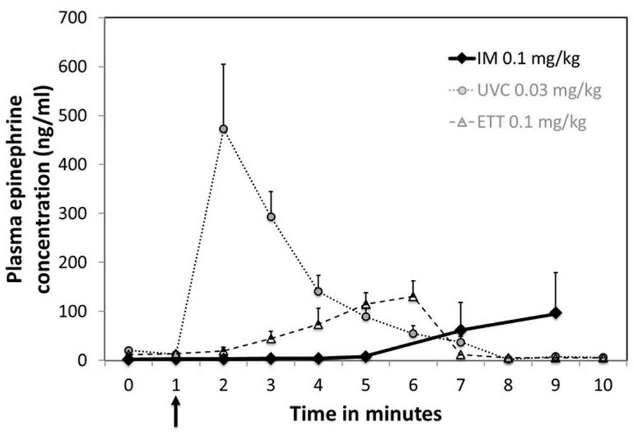

FIGURE 3 | Plasma concentrations following a single dose of IM epinephrine. Arrow indicates time of epinephrine administration. Data are mean ± SEM. Mean concentration for IM at 15 min was 216.2 ± 91.1 ng/mL. UVC and ETT concentration as previously published by Vali et al. (19) are included for comparison.

Return of Spontaneous Circulation (ROSC)

All 4 animals achieved ROSC with IM administration with time to ROSC at a median (range) of 3.95 (1.7–4.7) min. Mean carotid and pulmonary artery flows, systolic and diastolic blood pressures at and 2 min following ROSC are presented in **Table 2**.

DISCUSSION

Epinephrine is recommended in resuscitation algorithms utilized in well-resourced settings, with options for delivery *via* intravascular, intraosseous, and endotracheal routes. At present, the potential application of epinephrine in algorithms of care in less resourced environments, where the burden of asphyxia occurs, remains poorly defined. Complex routes of delivery limit broad use of this potentially life-saving medication as resuscitation in low resource settings (as taught in *Helping Babies Breathe* or the World Health Organization's *Essential Newborn Care*) would not include intubation or placement of umbilical or intraosseous access. In light of publications suggesting efficacy (18), we sought to investigate the concept of low cost, simplified delivery of epinephrine *via* intramuscular injection. However, our exploratory studies in a bovine asphyxia model evaluating pharmacokinetics with IM administration identified inadequate absorption of epinephrine until after ROSC. This result is consistent with hemodynamic redistribution that occurs with cardiac arrest and prioritization of perfusion to critical organs over peripheral tissues.

TABLE 2 | Hemodynamics at and following ROSC.

	ROSC	ROSC + 2 min
CA flow (ml/min)	11 ± 6	27 ± 13
PA flow (ml/min)	6 ± 3	37 ± 18
SBP (mm Hg)	56 ± 38	77 ± 25
DBP (mm Hg)	31 ± 22	55 ± 18

Mean ± SD of carotid (CA) and pulmonary (PA) artery blood flows, and systolic (SBP) and diastolic (DBP) blood pressures at and 2 min following ROSC.

Despite epinephrine's controversial impact on long term outcomes (25, 26), early administration has been shown to influence timing of ROSC in both animals and clinical models supporting our interest in simplified and efficient delivery (22, 27, 28). Animal studies further identify that chest compressions alone are inadequate in improving cerebral blood flow and that administration of epinephrine improves both coronary and cerebral perfusion with higher probability of ROSC (29–31). However, compromised infants can only benefit from administration of epinephrine if IV, IO or ET access can be obtained.

This scenario can occur in both resourced and low resourced settings. As example, a letter to the editor of *Resuscitation* described the use of IM epinephrine in an infant with perinatal asphyxia in Italy as access was not able to be obtained at the referral hospital (32). The infant received only IM epinephrine during resuscitation and survived without morbidity after severe perinatal acidosis. While it is unclear whether this dose of epinephrine influenced outcomes for this patient, this publication highlights the possibility and confirms that use of IM epinephrine has been considered in the stabilization of compromised newborns. We are unaware, however, of clinical settings where this is a common practice.

Additional data on the role of IM epinephrine in cardiopulmonary resuscitation exists from studies performed by Mauch et al. in a pediatric swine model of ropivacain-induced cardiac arrest (18). The authors report comparable rates of survival in pigs administered epinephrine by an IM route (0.1 mg/kg) as compared to IV dosing (0.01 mg/kg). In addition, they observed higher rates of survival and earlier return of spontaneous circulation (ROSC) with IM epinephrine as compared to normal saline controls. However, epinephrine concentrations were not evaluated in these studies. As our study failed to demonstrate absorption of epinephrine prior to ROSC with IM administration in asphyxia, the reported efficacy of this route in the piglet studies may be due to differences in the two models. Cardiopulmonary resuscitation (CPR) was initiated with the onset of circulatory arrest in the piglet model, with arrest defined as mean arterial pressures (MAP) of <25% of initial value, representing a clinically pulseless state. The piglets were unlikely to be as profoundly compromised, as our model utilizes a 5-min period of asystole. However, blood gases were not provided limiting our ability to compare the degree of asphyxia.

We speculate that the peripheral vasoconstriction associated with our model was less pronounced in the piglet study, facilitating perfusion and absorption of IM epinephrine during resuscitation. While our results imply IM epinephrine would be ineffective and risk delayed absorption and side effects, its role in the context of less profound asphyxia (including bradycardia without arrest) may still be worthy of evaluation.

Limitations of our model include the translation of findings in a lamb to human, with recognition of the potential contributions of hypovolemia and compromised cardiac glycogen stores in clinical settings (33, 34). This brief research study was also limited in it non-randomized design as studies were performed on extra, unassigned lambs as available. This approach has potential for selection bias as the experimental treatment was predetermined. In addition, only 4 studies were performed in this small, exploratory series. However, the results of our studies prior to ROSC were highly consistent, making it difficult to rationalize use of additional animals as added studies were not expected to influence our assessment of bioavailability. Similarly, this small exploratory study did not evaluate efficacy, impact on hemodynamics or ROSC, as these were all outcomes that did not seem appropriate to assess in absence of documented absorption. Finally, beyond concerns for late absorption, the safety of IM administration was not evaluated in our model. IM administration in the context of inadequate muscle perfusion risks local tissue injury and necrosis.

We would have anticipated delayed circulatory recovery, however the four animals achieved ROSC at a time comparable to that observed with ETT dosing, implying that effective CPR, rather than increased concentration of epinephrine, may have played a greater role in determining outcomes. Indeed, published studies in the ovine asphyxia model found that 6/13 animals achieved ROSC *prior* to administration of epinephrine when it was delayed to 6 min (35) and that epinephrine concentrations in absence of exogenous delivery was comparable to that observed with IM dosing (5–20 ng/mL) (22). It remains plausible that historical studies in UVC and ETT may have achieved ROSC in absence of epinephrine had it not been administered early (22). Indeed, hemodynamic data during chest compressions in the asphyxia model failed to demonstrate increase in systolic or diastolic blood pressure, or carotid blood flow following epinephrine administration with speculation that adenosine triphosphate depletion may contribute to the lack of effect (36, 37).

CONCLUSION

Studies in the neonatal ovine model suggest that inadequate absorption of epinephrine occurs with intramuscular administration during asphyxia. While a simplified route of delivery might be of interest, the lack of increase in epinephrine concentrations until several minutes after ROSC both questions the relevance of this route of administration as well as its safety. However, the bioavailability and efficacy of IM epinephrine in the context of less profound asphyxia may still warrant investigation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee at the State University of New York at Buffalo.

AUTHOR CONTRIBUTIONS

SB and SL: conceptualization. SB, SL, SG, and CK: methodology. SB, SL, and CK: formal analysis. SB, JN, SG, JH, CK, LN, PV, and SL: investigation and resources SB, PV, JN, and CK: data curation. SB: writing—original draft preparation. SB, JN, and SL: writing—review and editing. SG and CK: project administration. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.828130/full#supplementary-material

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ORIGINAL RESEARCH
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Errors in Antimicrobial Prescription and Administration in Very Low Birth Weight Neonates at a Tertiary South African Hospital

Sandi L. Holgate[1]*, *Adrie Bekker*[1], *Veshni Pillay-Fuentes Lorente*[2] *and Angela Dramowski*[1]

[1] Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, [2] Division of Clinical Pharmacology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Background: Antimicrobial prescription and administration-related errors occur frequently in very low birth weight (VLBW; <1,500 g) neonates treated for bloodstream infections (BSI).

Methods: Antimicrobial prescriptions for the treatment of laboratory-confirmed BSI were retrospectively analyzed for VLBW neonates at Tygerberg Hospital, Cape Town, South Africa (1 July 2018 - 31 December 2019), describing antimicrobial type, indication, duration of therapy and BSI outcomes. The prevalence of, and risk factors for prescription (dose, interval) and administration errors (hang-time, delayed/missed doses) were determined.

Results: One hundred and sixty-one BSI episodes [16 (9.9%)] early-onset, 145 [90.1%] healthcare-associated) affected 141 neonates (55% male, 25% born to mothers living with HIV, 46% <1,000 g birth weight) with 525 antimicrobial prescription episodes [median 3.0 (IQR 2–4) prescriptions/BSI episode]. The median duration of therapy for primary BSI, BSI-associated with meningitis and BSI-associated with surgical infections was 9, 22, and 28 days, respectively. The prevalence of dose and dosing interval errors was 15.6% (77/495) and 16.4% (81/495), respectively with prescription errors occurring most commonly for piperacillin-tazobactam and vancomycin given empirically. Administration errors were less frequent [3.8% (219/5,770) doses missed; 1.4% (78/5,770) delayed], however 64% had a hang-time (time from sepsis diagnosis to 1st dose of antimicrobial) exceeding 60 min. On multivariable analysis, postnatal age >7 days was associated with prescription errors ($p = 0.028$). The majority of neonates with BSI required escalation of respiratory support (52%) and 26% required intensive care admission. Despite fair concordance between empiric antimicrobial/s prescription and pathogen susceptibility (74.5%), BSI-attributable mortality in this cohort was 30.4%.

Conclusion: VLBW neonates with BSI's were critically ill and had high mortality rates. Hang-time to first antimicrobial administration was delayed in two-thirds of BSI episodes and prescription errors affected almost 1 in 6 prescriptions. Targets for intervention should include reducing hang-time, use of standardized antimicrobial dosing guidelines and implementation of antimicrobial stewardship recommendations.

Keywords: antimicrobial, prescription error, very low birth weight, neonatal sepsis, adverse event

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****Correspondence:***
Sandi L. Holgate
sandi@sun.ac.za

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INTRODUCTION

In Sub-Saharan Africa (SSA), ∼1 million deaths occur in the neonatal period annually (1), with prematurity, intrapartum related events and infection as the leading causes (2). The case fatality rate of 14% for bloodstream infections (BSI) (3) may be an underestimate given recent data suggesting that many neonatal deaths currently attributed to prematurity are actually caused by undetected infection, often with antimicrobial-resistant bacteria (4).

In SSA, gram negative organisms, with increasing antimicrobial resistance rates, predominate as causative pathogens for neonatal sepsis and meningitis (5–9). Due to limited availability of antimicrobials for resistant neonatal infections (10), it is of utmost importance to ensure antimicrobials are correctly used in this vulnerable population.

Evidence from sepsis trials in adult, pediatric and neonatal populations gave rise to the concept of the "golden hour", recommending receipt of the first dose of empiric antibiotic/s within 1 h of presentation to improve sepsis outcomes (11, 12).

Physiology in the neonatal period is constantly changing and developing requiring frequent dose and interval changes to achieve adequate drug concentrations. These physiological changes may affect the pharmacokinetics and pharmacodynamics of drugs resulting in the need for dosing adjustments in accordance with age, weight and/or body surface area (13–15), increasing the potential for prescribing errors.

Neonates, particularly those in the intensive care setting, are at high risk of medication errors (16–18), many due to poor prescribing (19). Antimicrobials are among the most common drug classes to be associated with medication errors (20–22), with up to a third resulting in harm to the patient (21). Dosing errors, inappropriate antimicrobial for the underlying condition, premature cessation, laboratory monitoring errors and therapeutic duplication are frequent errors, with vancomycin and piperacillin-tazobactam being the agents most commonly associated with prescription errors (23). Some antimicrobials (e.g., aminoglycosides and vancomycin) have toxic side effects and a narrow therapeutic index (24), necessitating therapeutic drug monitoring (TDM) to protect patients from these harms, and guide optimal and adequate antimicrobial dosing (25).

Given the limited data from SSA regarding this widespread problem we reviewed the prevalence of, and contributors to, antimicrobial prescription and administration errors in very low birth weight (VLBW: <1,500 g) neonates with laboratory-confirmed BSI episodes at a large South African neonatal unit.

METHODS

Study Design and Population

We conducted a retrospective, descriptive study of antimicrobial prescription- and administration-related errors in VLBW neonates with laboratory-confirmed bacterial and fungal BSI at Tygerberg Hospital, Cape Town, South Africa between 1 July 2018 and 31 December 2019. Inborn neonates with a birthweight of 500–1,500 g who developed culture-confirmed bloodstream infection during their hospital stay were eligible for inclusion. This weight band was selected due to the higher number of BSI's seen in this group (26) and complexity in prescribing for smaller neonates. BSI was diagnosed by incubating at least 1 ml of aseptically collected blood into BacT/Alert PF Plus bottles (Biomérieux, Marcy l'Ètoile, France). Study exclusion criteria were: patients transferred in from outlying facilities as antimicrobials may have been administered before transfer; neonates with growth of pathogens on urine, tracheal aspirate or wound swab cultures only; neonates with blood and cerebrospinal fluid (CSF) cultures isolating contaminants as defined by the United States Centre for Disease Control and Prevention list of commensal flora (27), and neonates receiving antiviral medications.

Study Setting

Tygerberg Hospital is the tertiary referral hospital for sick and/or preterm neonates requiring specialist medical and/or surgical care in Cape Town's Metro East. The neonatal unit comprises four 30-bed wards and a 12-bed medical and surgical neonatal intensive care unit (NICU), with a 132-bed total capacity and occupancy rates averaging 93%. Owing to a shortage of NICU beds in the Western Cape Province, a provincial periviability policy was developed to guide decisions on eligibility for NICU admission (generally >800 g and >27 weeks gestation) (28). Standard practice in this setting is for all sick and/or preterm neonates to be admitted into a high care ward where respiratory support such as nasal continuous airways pressure (nCPAP) or high flow nasal cannula can be initiated, surfactant administered, intercostal drains inserted and central lines placed for total parenteral nutrition (TPN) if needed. NICU is reserved for neonates requiring mechanical ventilation, therapeutic hypothermia or inotropic support.

Empiric Antimicrobial Therapy for Neonatal Infections

For early onset (within 72 h of birth) sepsis, ampicillin and gentamicin are the empiric antimicrobial of choice. In neonates older than 72 h of life where healthcare-associated infection (HAI) is suspected (26), piperacillin-tazobactam plus amikacin is recommended, unless the baby is clinically unstable or there is a clinical suspicion of a gram negative infection or meningitis. In these cases, meropenem is recommended to provide cover for antimicrobial resistant pathogens and to enhance CSF penetration. Vancomycin is added if the neonate has or had a central venous catheter inserted or if a skin or soft tissue infection is present, where methicillin-resistant *S. aureus* is a likely pathogen. Antifungal therapy is added where clinically indicated and colistin is used in cases where a carbapenem-resistant organism is very likely (empiric therapy) and/or microbiologically-confirmed (targeted therapy). Antimicrobial prescriptions are written by all levels of medical doctors, from juniors (medical officers and residents) to seniors (fellows, consultant Pediatricians and neonatologists). A specific antimicrobial prescription chart is used which allows for the drug name, dose, route of administration, frequency, start and stop date and the prescribing doctors name and signature. Registered nurses are responsible for preparing and administering the antimicrobials. All antimicrobial therapy for bloodstream infection is administered intravenously in this population.

Therapeutic Drug Monitoring for Antimicrobial Agents

Locally, trough TDM is recommended before the 3rd dose of gentamicin and amikacin to limit potential toxicities (29). In mid-2019 local vancomycin dosing guidelines were changed to recommend a loading dose of vancomycin followed by maintenance doses which vary according to gestational age in preterm infants (29). Prior to this change TDM was recommended before the 4th dose, whereas later TDM samples were recommended before administration of the 3rd or 4th vancomycin dose. When reviewing the prescriptions, decision regarding correct timing of the TDM was based on whether the loading dose was given. The Division of Clinical Pharmacology uses DoseMeRx software (30) to predict vancomycin dose based on gestational age, weight, change in creatinine concentration and a vancomycin trough concentration.

Study Objectives and Definitions

Our primary objective was to determine the prevalence of antimicrobial-related medication errors in VLBW neonates with laboratory-confirmed BSI. Duplicate BSI pathogens isolated within 10 days of the first positive culture, were considered to represent a single infection episode. Coagulase-negative staphylococci (CoNS) were considered to be pathogens, if 2 or more CoNS were isolated from blood cultures drawn within two consecutive days. Data were analyzed comparing neonates with early onset sepsis (EOS) to those with healthcare-associated BSI (HA-BSI episodes that developed >72 h after admission to hospital).

For clinical impact of the BSI event we described: escalation of respiratory support and/or need for mechanical ventilation, admission to NICU, inotropic support (24 h prior to and up to 72 h after sepsis diagnosis) and need for blood products or surgery during antimicrobial therapy. In a study population such as VLBW neonates, where co-morbitidies may be high, BSI attributable death [death within 72 h of BSI (31)] was compared to those who died more than 72 h after the blood culture (BSI associated death) in attempt to clarify the contribution of the BSI to the mortality rate (32).

The indication for antmicrobials and the overall antimicrobial treatment duration was determined. We calculated the frequency of dose errors (a 10% cut off margin on either side of the ideal dose was used) (33), dosing interval errors and missed or delayed (>1 h) antimicrobial doses. Two local reference books, compiled from international literature by the two tertiary hosipatls in the Western Cape were used (29, 34). We also determined the hang-time (interval from clinical infection diagnosis, based on the time of blood culture sampling, to administration of the first dose of antimicrobial) to empiric and concordant antimicrobial therapy. One hour was used as a target hang-time based on the increased mortality associated with every hour delay in initiating appropriate antimicrobials (11). Cases where death occurred before antimicrobial administration and where the first dose of antimicrobial was documented as given before infection diagnosis were excluded from the hang-time analysis. The proportion of discordant empiric antimicrobial prescriptions was described i.e., mismatch between the pathogen identified and its sensitivity profiles to the empiric antimicrobial prescribed. We described the proportion of antimicrobial prescription episodes where TDM sampling was not performed at the recommended time, according to the local guidelines. For this we reviewed notations on the prescription chart in combination with data from the pharmacology laboratory. We assessed the proportion of TDM values in the therapeutic drug concentration range and proportion of TDM episodes where dose adjustments were enacted (if required). In cases where there was more than 1 prescription for vancomycin per BSI, repeat prescriptions were not analyzed for prescription errors as dose or interval changes may have been made according to TDM recommendations.

Data Sources

Data were collated from the Tygerberg Hospital Vermont Oxford Network neonatal database, the hospital's electronic record management system, the National Health Laboratory Service (NHLS), Tygerberg Hospital Clinical Pharmacology Laboratory and Unit for Infection Prevention and Control's neonatal BSI surveillance records. Patient records were reviewed to collect demographic, clinical, laboratory and antimicrobial prescription data. Data were entered into an institutional-hosted REDCap (Research Electronic Data Capture) database (35).

Statistical Analysis

The sample size required to deliver a 95% confidence interval with a + or – 5% margin of error at an estimated prescribing/administration error prevalence of 20% was calculated at 111 patients with infection episodes. Descriptive analyses of neonatal and maternal demographic characteristics were performed. Continuous variables (e.g., days of antibiotic therapy) were reported as median with interquartile ranges (IQR), and categorical data (e.g., missed antibiotic doses) were reported as proportions/percentages. Students *t*-test, Pearson's chi squared test and other non-parametric tests (e.g., Fishers Exact) were used for hypothesis testing where appropriate. Demographic factors associated with prescription errors were evaluated using a multivariate binomial regression model where significant univariate predictors were added at a *p*-value of 0.2 to inform the multivariate model. For all statistical tests performed, a *p*-value <0.05 was considered significant. All the statistical analyses were performed using STATA 16.0 (College Station, Texas 77845, USA).

Ethics approval for this study was received from the Stellenbosch University Health Research Ethics Committee, reference number N19/12/159 and Tygerberg Hospital via the National Health Research Ethics Committee.

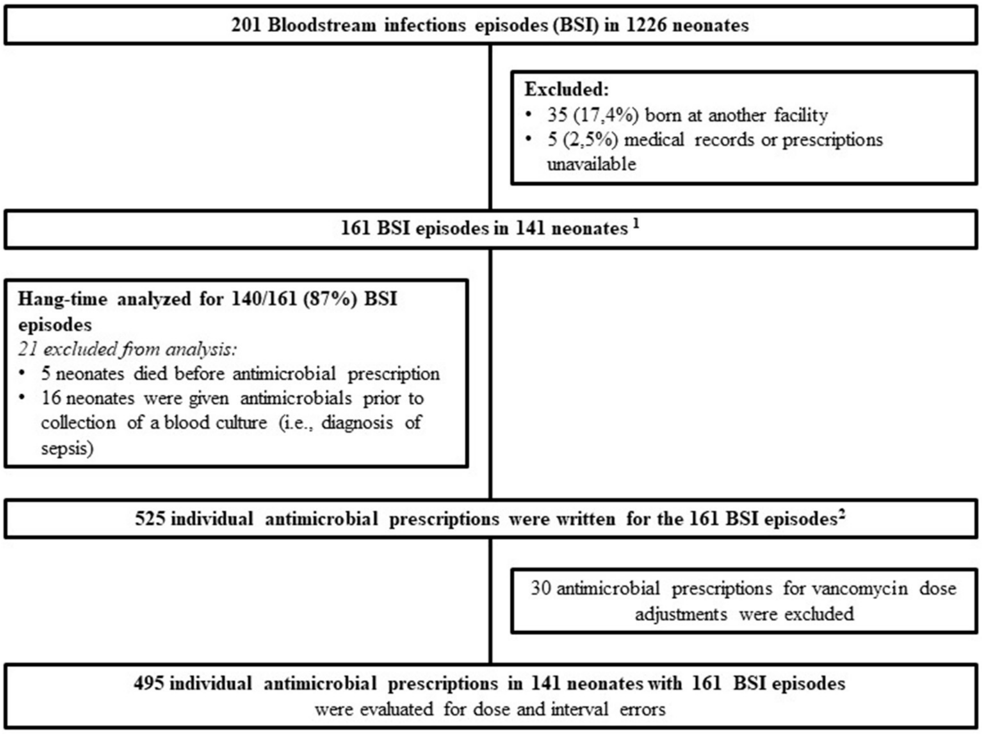

FIGURE 1 | Culture confirmed blood stream infection episodes and prescriptions in very low birth weight neonates from 1 July 2018 to 31 December 2019. [1] 141 neonates: 15 with 2 BSI episodes, 1 with 3 BSI episodes and 1 with 4 BSI episodes. [2] Missed and delayed doses were evaluated on all 525 prescriptions with the denominator being the total number of doses administered.

RESULTS

Maternal and Neonatal Characteristics

Two-hundred and one laboratory confirmed BSI episodes were identified in 1,226 VLBW neonates admitted to Tygerberg Hospital during the study period. Antimicrobial prescriptions were analyzed for 161 BSI episodes diagnosed in 141 neonates (**Figure 1**). The median gestational age and birth weight were 28 weeks and 1,030 g with a male predominance (78; 55.3%) (**Table 1**). A quarter of mothers were living with HIV. Forty four percent (62/141) went into spontaneous preterm labor and the remainder delivered following induction of labor or cesarean section for maternal indications. Of the 161 BSI episodes, the majority were healthcare associated (145; 90%) and occurred at a median of 10 (IQR 7–21) days of life (**Table 2**).

Blood Stream Infection Episodes

Most BSI episodes were primary (no identifiable source) (94; 58.4%), with the remaining 67 (41.6%) comprising BSI with either meningitis, necrotising enterocolitis or other surgical source and catheter-associated BSI. Gram negative BSI pathogens predominated [117; 72.7%; 37% (59/161) Klebsiella species, 17% (26/161) *Serratia marcescens*], followed by gram positives [41; 25.5%; 16% (25/161) *Staphlococcus aureus*] and fungi (3; 1.9%). More than half (52%) of neonates needed escalation of respiratory support and 26% required admission to NICU. An additional 11% (18/161) were already admitted in the NICU at the time of the sepsis diagnosis. Thirty percent of BSI episodes (49/161) resulted in death within 72 h of the sepsis diagnosis, with a median (IQR) interval from blood culture collection to death of 1 (0–2) day.

Prescription Episodes

A total of 525 individual antimicrobial prescriptions were identified for the 161 neonatal, including re-prescribing for dose and/or dosing interval changes (**Table 2**). A median of 3 (IQR 2–4) individual antimicrobial prescriptions were observed for each neonatal BSI episode. The median number of antimicrobial classes prescribed per episode was 3 (IQR 2–4), however fewer classes of antimicrobial were prescribed in the EOS group [median 2 (IQR 2–3) vs. 3 (IQR 2–4) in those with HA-BSI]. The median duration of antimicrobial therapy was shortest for primary BSI and longest for BSI associated with meningitis and surgical infections at 9, 22, and 28 days, respectively. In three-quarters of BSI episodes, the empiric antimicrobial therapy prescribed was concordant with the antimicrobial susceptibility of the BSI pathogen isolated (120; 74.5%). Discordance between pathogen and empiric antimicrobial did not significantly impact sepsis attributable mortality rates [9/44 (20%) vs. 27/112 (24%), $p = 0.6$, OR 0.8 (95% CI 0.3–1.9)] or 30 day mortality rates [11/58 (19%) vs. 25/98 (26%), $p = 0.3$. OR 0.7 (CI 0.3–1.5)].

Hang-Time

Of the 161 BSI episodes included in the analysis, hang-time could only be determined for 140 (87%) BSI episodes, as 5 neonates died before AMO could be prescribed and in 16 neonates the AMO was administered prior to the diagnosis of sepsis. The median antimicrobial hang-time was 115 (IQR 48–210) min and did not differ by infection type (EOS vs. HA-BSI) (**Table 3**). Only 51/140 (36.4%) evaluable neonatal BSI episodes had administration of the first dose of empiric antimicrobials within 60 min. There was no difference in the proportion of neonatal BSI episodes with hang-time <60 min by BSI type [4/14 (28.6%) of EOS vs. 47/127 (37.0%) of HA-BSI; $p = 0.770$]. Furthermore, hang-time of <60 min was not associated with a reduced risk of sepsis attributable death [16/42 (38%) vs. 33/98 (36%); $p = 0.789$, OR 1.1 (95% CI 0.5–2.3)].

Prescription and Administration Errors

After excluding neonatal BSI epsiodes where changes to vancomycin prescriptions were needed based on TDM results ($n = 30$), 495 prescription episodes remained for analysis of dose and dose interval errors. Dose [0/46 (0%) EOS vs. 77/449 (17.2%) HA-BSI, $p = 0.001$] and dosing interval [3/46 (6.55) EOS vs. 78/449 (17.4%) HA-BSI, $p = 0.037$] prescription errors occurred significantly more frequently among neonates with HA-BSI than EOS (**Table 3**). Of the antimicrobials prescribed as empiric therapy for suspected BSI, vancomycin had the highest frequency of dosing errors (30.6%), whereas piperacillin-tazobactam had the highest frequency of dose interval errors (40.5%) (**Table 4**). Of the 495 prescriptions analyzed, 33 (6.7%) had inappropriately high doses and 44 (8.9%) had low doses. There were no incorrect doses in the prescriptions for EOS and only 3 dose interval errors in this group. Postnatal age > 7 days, compared to those older than 7 days, was the only significant factor associated with prescription errors [adjusted odds ratio 2.64 (95% CI 1.2–6.3); $p = 0.028$] (**Table 5**). Among all prescriptions, there were 219 (3.8%) missed doses and 78 (1.4%) delayed doses: 12 (3.5%) were delayed in the EOS group vs. 66 (1.2%) in the HA-BSI group; $p = 0.001$. We assessed gestational age, weight at the time of BSA, postnatal age in days and timing of infection as possible factors associated with admin errors but none were deemed significant. Compliance with adherence to TDM recommendations was variable: 85% for vancomycin; 30% for amikacin and 13% for gentamicin (**Table 6**).

TABLE 1 | Characteristics of mothers and very low birth weight neonates receiving antimicrobials for blood stream infection episodes ($n = 141$).

Characteristic	Total neonates $N = 141$
Sex, male, *n* (%)	78 (55.3)
Gestational age at birth in weeks, median (IQR)	28 (27–29)
Birth weight in grams, median (IQR)	1,030 (895–1,160)
Birthweight categories	
500–749 g, *n* (%)	10 (7.1)
750–999 g, *n* (%)	55 (39)
1,000–1,249 g, *n* (%)	54 (38.3)
1,250–1,500 g, *n* (%)	22 (15.6)
Mode of delivery	
Normal vertex delivery, *n* (%)	46 (32.6)
Cesarean section, *n* (%)	95 (67.4)
Mother attended antenatal care[a], *n* (%)	132 (93.6)
Maternal HIV status	
HIV-negative, *n* (%)	103 (73.1)
Women living with HIV, on antiretroviral therapy (ART), *n* (%)	35 (24.8)
Women living with HIV, not on ART, *n* (%)	1 (0.7)
HIV status unknown, *n* (%)	2 (1.4)
Maternal complications and treatment	
Any antenatal steroids received, *n* (%)	127 (90.1)
Maternal chorioamnionitis, *n* (%)	2 (1.4)
Maternal urinary tract infection, *n* (%)	7 (5.0)
Spontaneous preterm labor, *n* (%)	62 (44.0)
Prolonged rupture of membranes (>18 h), *n* (%)	23 (16.3)

[a]Maternal antenatal care was defined as documented attendance of any prenatal obstetric care prior to delivery. IQR, interquartile range.

DISCUSSION

In this cohort of 141 hospitalized VLBW neonates with BSI, we evaluated the prevalence of antimicrobial prescription and administration-related errors for 495 prescriptions. Median hang-time to the first dose of empiric antimicrobial was prolonged beyond 60-min in 64% of prescriptions. Prescription errors (15.6% for dose and 16.4% for interval) were 4-fold more prevalent than administration errors (1.4% had delayed doses and 3.8% had missed doses), particularly in neonates >7 days postnatal age. Prescription errors were frequent for vancomycin (dose errors) and piperacillin-tazobactam (dose interval errors). There was moderate concordance between pathogen susceptibility and empiric antimicrobial choice (75%).

BSI- attributable mortality occurred in almost one-third of neonates (49/141, 30.4%). This is in keeping with a crude mortality of 29% in VLBW infants at Tygerberg hospital in 2015 (5), but much higher than the BSI-attributable neonatal mortality observed in in Taiwan (7%) and China (5–14%) (31, 36). These studies included term and preterm infants, with a predominance of gram positive organisms pathogens. Reasons for the substantially higher BSI-attributable mortality rates at our institution may include: a greater proportion of fulminant gram negative BSI, higher rates of antimicrobial resistance, a greater percentage of preterm neonates with immature immunity (46% of our cohort weighed < 1,000 g at birth) and local guidelines that limit access to NICU care for babies with birth weight <800 g (28). A large German study confirmed that gram negative pathogens are associated with higher mortality in VLBW neonates compared to infection with gram-positive organisms (37). Their crude mortality of 5.7% is significantly lower than ours, but only 16% of BSI's were caused by gram-negative organisms in their cohort compared to 73% in our study.

The duration of antimicrobial therapy at our unit was 9 days for primary BSI, but substantially longer in neonates with meningitis and surgical infections. In a systematic review of

TABLE 2 | Antimicrobial therapy and impact of blood stream infection episodes (161 episodes in 141 neonates)—a comparison between early onset and healthcare associated BSI.

Antimicrobial therapy and impact	Total BSI episodes *N* = 161	Early-onset BSI episodes *N* = 16	Healthcare-associated BSI episodes *N* = 145	*P*-value
Age in days at infection onset, median (IQR)	10 (6–18)	0 (0–2)	10 (7–21)	N/A
Indication for antimicrobials, *n* (%)				
Primary BSI	94 (58.4)	11 (68.8)	83 (57.2)	N/A
BSI with proven meningitis	14 (7.7)	2 (12.5)	12 (8.3)	
BSI with necrotising enterocolitis	27 (16.8)	0 (0)	27 (18.6)	
BSI with catheter associated sepsis[a]	16 (9.9)	3 (18.8)	13 (9.0)	
BSI with other surgical source[b]	5 (3.1)	0 (0)	5 (3.4)	
More than 1 infection[c]	5 (3.1)	0 (0)	5 (3.4)	
Duration of antimicrobial therapy course for infection episodes (days), median (IQR)[d]				
Primary BSI	9 (5–13)	9 (5–10)	9 (6–14)	N/A
BSI with proven meningitis	22 (18–24)	19 (14–24)	22 (19.5–24.5)	
BSI with necrotising enterocolitis	2 (1–8)	–	2 (1–8)	
BSI with catheter associated sepsis[a]	10 (2–13)	1 (1–11)	10 (2–13.5)	
BSI with other surgical source[b]	28 (7–31)	–	28 (7–31)	
More than 1 infection[c]	22 (21–23)	–	22 (21–23)	
Impact of BSI episode[e], *n* (%)				
Required escalation of respiratory support	84 (52.2)	5 (31.3)	79 (54.5)	N/A
Required NICU admission from HC ward	42(26.1)	5 (31.3)	37 (25.5)	
Required mechanical ventilation[f]	58 (36.0)	6 (37.5)	52 (35.9)	
Required inotropes	32 (19.9)	5 (31.3)	27 (18.6)	
Required blood products[g]	65 (40.4)	2 (12.5)	63 (43.4)	
Required surgery[g]	9 (5.6)	0 (0)	9 (6.2)	
Outcome of BSI episodes, *n* (%)				
Died within 72 h (BSI-attributable deaths)	49 (30.4)	6 (37.5)	43 (27.7)	0.57
Antimicrobial prescriptions				
Antimicrobial prescriptions for culture-confirmed BSI episodes, *n*	525	46	479	–
Antimicrobials prescribed per BSI episode, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	–
Appropriateness of the empiric prescription, *n* (%)				
Concordant[h]	120 (74.5)	12 (75.0)	108 (74.5)	0.524
Discordant	36 (22.4)	2 (12.5)	34 (23.4)	
Died prior to receiving antimicrobial therapy	5 (3.1)	2 (12.5)	3 (2.1)	

BSI, blood stream infection; SD, standard deviation; IQR, interquartile range; NICU, neonatal intensive care unit; HC, high care.
[a]*Catheter associated sepsis = a neonate with clinical signs of sepsis plus a positive blood culture in the period between catheter insertion and 48 h post removal, with no other focus of sepsis.*
[b]*Five patients had non-NEC surgery e.g., joint aspiration for septic arthritis.*
[c]*More than 1 infection was when there was more than 1 source e.g., meningitis plus NEC.*
[d]*Those where patient demised before the 1st dose of antimicrobial could be administered were excluded.*
[e]*Escalation of care within 24 h before and 72 h after the positive blood culture.*
[f]*Includes those on mechanical ventilation at the time of sepsis diagnosis.*
[g]*Need for blood products or surgery at any time while the neonate was receiving antimicrobials.*
[h]*Concordance was when the organism cultured was sensitive to the empiric antibiotic prescribed.*

optimal antibiotic duration in children, 10 days of intravenous treatment is suggested for bacteraemia caused by gram negative organisms and 7–14 days for Staphylococcal infections (38). In many neonatal units there is substantial variability in duration of antimicrobial therapy for infection, and this is a potential target for antimicrobial stewardship to standardize, and where safe to do so, reduce length of therapy (39).

The potential for adverse drug events in neonates is high, especially for patients in the NICU, with 79% occurring at the stage of drug prescribing and 34% involving incorrect dosing in one American study (40). In children, prescribing errors are more commonly found with antimicrobials than other agents (20, 22, 41) possibly due to the fact that, along with sedatives, they are the most common class of drug prescribed (20). This was confirmed locally in a study from Gauteng including NICU patients as well as pediatric inpatients, where 43% of errors were related to anti-infective agents (21). Almost 20% of antimicrobial prescriptions had dose errors with 18.9% frequency errors in a

TABLE 3 | Antimicrobial prescription errors and hang-time.

Prescription errors and hang-time	Total prescription episodes *N* = 495	Prescription episodes for early-onset BSI *N* = 46	Prescription episodes for healthcare-associated BSI *N* = 449	*P*- value
Antimicrobials prescribed with incorrect dosage[a], *n* (%)	77 (15.6)	0 (0%)	77 (17.2)	0.001
Antimicrobials prescribed with incorrect dosing interval[a], *n* (%)	81 (16.4)	3 (6.5)	78 (17.4)	0.037
Hang-time in minutes to receipt of empiric antimicrobial/s, median (IQR)[b]	115 (48–210)	109.5 (13–120)	115 (50–240)	0.298
Hang-time in minutes to receipt of concordant antimicrobial, median (IQR)[b]	150 (60–658)	110 (53–140)	170 (60–790)	0.090

[a]*Where there was >1 prescription episode for vancomycin the subsequent prescriptions were excluded as adjustments may have been made according to the therapeutic drug monitoring.*
[b]*Patients who died before antimicrobials could be given and those where antimicrobial was recorded as given before the blood culture was taken were excluded from the hang time analysis.*
IQR, interquartile range; BSI, bloodstream infections.

TABLE 4 | Frequency of dosing and dosing interval errors for frequently used antimicrobials.

Antimicrobial name[a]	Number of prescriptions	Frequency of dose errors, *n* (%)	Frequency of dose interval errors *n* (%)
Ampicillin	30	0 (0)	6 (20.0)
Amikacin	78	18 (23.1)	3 (3.8)
Cefazolin	8	6 (75.0)	8 (100)
Cefotaxime	9	3 (33.3)	4 (44.4)
Colistin	21	7 (33.3)	3 (14.3)
Fluconazole	17	2 (11.8)	0 (0)
Gentamicin	14	1 (7.1)	0 (0)
Imipenem	5	1 (20.0)	3 (60.0)
Linezolid	5	1 (20.0)	1 (20.0)
Meropenem	136	5 (3.7)	1 (0.7)
Piperacillin-tazobactam	79	2 (2.5)	32 (40.5)
Trimethoprim/sulfamethoxazole	10	5 (55.6)	3 (33.3)
Vancomycin	72	22 (30.6)	15 (20.8)

[a]*Antimicrobials with fewer than five prescription episodes were excluded (amphotericin B, cephalexin, cefepime, ceftriaxone, cefuroxime, ciprofloxacin, clindamycin, ertapenem, penicillin G, rifampicin, tobramycin).*

TABLE 5 | Predictors of antimicrobial prescription errors in very low birth weight neonates.

Variable	Unadjusted Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
Gestational age		
≥28 weeks	0.7 (0.36–1.34)	–
Highest weight at time of BSI		
≥1,000 g	0.8 (0.4–1.6)	–
Postnatal age		
≥7 days	3 (1.4–6.3)	2.64 (1.17–6.29)
Timing of infection		
Healthcare-associated BSI*	3.2 (0.9–10.7)	1.47 (0.36–5.95)

BSI, bloodstream infections; CI, confidence interval.
Healthcare-associated BSI was compared to early onset sepsis.

pediatric study in Pakistan (42). The error rates in our VLBW neonatal population are comparable, although slightly lower, at 15.6 and 16.4%, respectively. Our study shows 42% of dose errors were associated with high doses and 57% with low doses. These findings were similar to a French study which reported 46% high dose errors and 54% low dose errors (43).

A Brazilian study noted that in general, prescribing errors are more frequent in preterm neonates with dosing errors occurring in 18.5% of preterm neonates compared to 12.9% in term neonates (18). These rates are still higher than those seen in manual prescriptions for preterm infants, <33 weeks, in France (43) where they subsequently recommended the use of computerized systems for prescribing in neonatal units. Electronic prescriptions in children were studied by Maat et al. and they found that the use of a "standardized structured template" reduced the risk of errors compared to "free text" prescriptions (44). Our unit does not currently have access to electronic prescribing systems, however more simple interventions such as preformatted prescription sheets, training, pharmacist-led prescription reviews and the use of a single reference source have been successful in reducing prescription errors (17, 19, 45, 46). No single intervention to reduce medication errors has

TABLE 6 | Therapeutic drug monitoring (TDM) of selected antimicrobials for neonatal BSI episodes.

	n (%)
Vancomycin	
TDM performed if clinically indicated[a]	39/46 (84.7%)
TDM performed at the correct time[b]	16/39 (41.0%)
Vancomycin drug concentration[c]	
Toxic	6 (15.4%)
Sub-therapeutic	19 (48.7%)
Appropriate	14 (35.9%)
Dosing adjusted following toxic/sub-therapeutic level	15/25 (60.0%)
Vancomycin stopped[f] following toxic/sub-therapeutic level	6/25 (24%)
Amikacin	
TDM performed if clinically indicated[d]	8/27 (29.6%)
TDM performed at the correct time[e]	2/8 (25.0%)
Amikacin trough concentration	
<2.5 μg/mL	3 (37.5%)
2.5–5 μg/mL	4 (50.0%)
>5 μg/mL	1 (12.5%)
Amikacin stopped[f] following trough concentration >2.5 μg/mL	4/5 (80%)
Gentamicin	
TDM performed if clinically indicated[d]	1/8 (12.5%)
TDM performed at the correct time[e]	0/1 (0.0%)
Gentamicin trough concentration	
<1 μg/mL	0 (0.0%)
1–2 μg/mL	0 (0.0%)
>2 μg/mL	1 (100%)
Gentamycin stopped[f] following trough concentration>2 μg/mL	1/1 (100%)

[a] *TDM was indicated in any patient where ≥4 doses of vancomycin were administered.*
[b] *Prior to the 4th dose of vancomycin administration or, if loading dose given, prior to the 3rd or 4th dose of vancomycin administration.*
[c] *Toxic > 20 μg/mL; sub therapeutic <10 μg/mL; appropriate 10–20 μg/mL.*
[d] *Any patient where ≥3 doses of amikacin or gentamicin were administered.*
[e] *Prior to the 3rd dose of amikacin or gentamicin administration.*
[f] *Drug stopped within 24 h of TDM sample.*

been proven to be superior, thus individual units need to implement what is practical and cost-effective in their setting (47).

The only factor that was associated with prescription errors in our cohort was a postnatal age of 7 days or more, where prescriptions for HA-BSI necessitate use of a wider range of antimicrobials, some of which are not commonly used. In addition, some antimicrobial dosing intervals change with increasing postnatal age, necessitating accurate calculation by the prescriber which increases risk of errors. Another factor that may have contributed to confusion among prescribers, is the use of two different neonatal prescribing guidelines, which did not include recommendations for at least three antimicrobials used in our unit. Many doctors work at both tertiary hospitals in the Western Cape and their respective referral hospitals and thus reference books are shared between the units. Development of a single drug dose reference book for all provincial neonatal units should be considered to minimize prescription errors.

Studies in adults and children have focused on the concept of the golden hour for initiation of antimicrobial treatment in patients with sepsis (11). In our study, the median hang-time to empiric antimicrobial was close to 2 h for both early-onset BSI and HA-BSI. In the EOS group, delays in admitting neonates from labor ward or theater may have been a contributing factor. In patients with HAI, difficulty obtaining intravenous access and poor communication between medical and nursing staff may have contributed to prolonged hang-times. In our neonatal wards there are limited number of registered nurses able to administer medication, thus if the sepsis diagnosis is not directly communicated to them, there is an increased chance that they will only come across the medication chart when doing their medication rounds. In a quality improvement study in South Carolina, improved communication successfully reduced antimicrobial hang-time in neonatal HAI (48). In contrast to our findings, a NICU sepsis study found prolonged hang-time was an independent risk factor for death (12). However, their patients were bigger (mean birth weight 2.3 kg, mean GA 34 weeks), and isolated mostly gram positive pathogens. In our setting and in Germany gram negative infections have shown significant association with mortality (5, 37). Possible reasons for the failure to find an association between hang-time and mortality in our cohort may be the small sample size and the predominance of gram negative BSI pathogens with a fulminant disease course, despite prompt administration of antimicrobials.

Cook et al. showed that neonates and children receiving discordant empiric antibiotics had a 3-fold higher risk of death within 30 days of BSI (49) but this was not found in our study. Only 15.5% of their cohort were preterm neonates. Death within 72 h of sepsis diagnosis was not significantly higher in our patients who received discordant empiric therapy. Although not significant, there appeared to be a longer delay in initiating concordant therapy in HA-BSI episodes, likely due to higher rates of antimicrobial resistance. Most antimicrobials are kept as ward stock for rapid access, however in some cases of less commonly used antimicrobials (e.g., linezolid, imipenem), delays may occur while waiting for pharmacy to issue the drugs or whilst awaiting permission from the antimicrobial stewardship committee (e.g., colistin).

In a review of medication incidents in England and Wales, omitted and delayed doses were the most common category of error reported (50). Comparatively the percentage of missed and delayed antimicrobial doses in this study was low at 3.8 and 1.4%, respectively. This may be a spurious finding as antimicrobial administration was not observed in our study. Thus, correlation between doses signed for and the actual time of administration could not be confirmed. In a busy neonatal unit with low nurse-to-patient ratios, one could postulate that antimicrobials with less frequent dosing would have fewer administration errors. This is in keeping with our once daily aminoglycoside dose recommendation.

In this study, although vancomycin TDM was done regularly, it was only done at the recommended time in 41% of cases. This may have been due to limited staff availability after hours to collect blood samples or, to cluster blood sampling to minimize the number of neonatal invasive procedures. Additionally, vancomycin dose adjustments often require regular consultations with clinical pharmacologists whose services are only available in large, academic centers contributing to inadequate dosing/ dosing errors. The aminoglycoside TDM was less well-performed and is an area where management can be improved. Medical and nursing staff training, close review of prescription charts on ward rounds and antimicrobial stewardship rounds, and inclusion of TDM recommendations in antimicrobial guidelines and unit protocols should be implemented.

This study has several limitations including a retrospective design, unavailability of some prescription charts (2.5%) and the lack of documentation of time of BSI diagnosis in the clinical notes (time of blood culture sampling recorded on the laboratory information system was used as a proxy). However, this resulted in some episodes where antimicrobials appeared to have been given before infection diagnosis, and were thus excluded from the hang-time analysis. In addition, we were unable to identify time of prescription (day/night) and the seniority of the prescribing doctor as that information is not currently captured on our antimicrobial prescription charts. One might postulate that junior doctors may be more prone to prescribing errors, or that after-hours, when there is less support, errors may be more frequent. The quality of the drug prescription in terms of legibility, unspecified data etc was not described as a standardized, structured prescription chart is used to reduce these issues. Information regarding whether antimicrobials were administered in the wards vs. the NICU, with potentially better nurse to patient ratios, was also not available. As the study was retrospective, the preparation and administration of drugs was not observed, thus the accuracy of antimicrobial time of administration could not be confirmed, which may account for the low frequency of administration errors. The strength of this study, however, lies in the large number of prescriptions analyzed and the detailed analysis of several prescription related metrics. In addition there is very limited data available for this population (VLBW neonates with BSI from SSA), a group known to be at higher risk of BSI. This study provides novel data and comprehensive analysis to address this gap. The findings of this study could potentially guide other neonatal units facing similar challenges with antimicrobial prescription and administration.

CONCLUSION

Although antimicrobial prescription and administration errors are prevalent in this vulnerable population of VLBW neonates, the frequency of errors is similar to that reported from other lower and upper-middle income countries (LMIC). However, the rates are higher than that observed in high income countries. Further studies are needed to identify and measure the impact of future interventions to reduce antimicrobial prescribing and administration errors in resource-limited neonatal units. Potential prescribing interventions could include use of a standardized antimicrobial reference guide, improved communication to decrease hang-time, more detailed prescription charts, pharmacist-led prescription review and antimicrobial stewardship interventions to reduce duration of therapy and minimize dosing errors.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stellenbosch University Health Research Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The study was conceptualized by SH and AD. All data collection was done by SH. All authors contributed to the data analysis and manuscript preparation and have read and approved the final manuscript.

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A Family-Centered, Multidisciplinary Clinic for Early Diagnosis of Neurodevelopmental Impairment and Cerebral Palsy in China—A Pilot Observation

Hai-Bo Huang[1], Man Joe Watt[1,2,3], Matthew Hicks[4], Qian-Shen Zhang[1], Fang Lin[1], Xue-Qing Wan[1], Chun-Bong Chow[1] and Po-Yin Cheung[1,4] on behalf of the MDAC program[1,5]*

[1] Department of Pediatrics, University of Hong Kong-Shenzhen Hospital, Shenzhen, China, [2] Department of Pediatrics, Glenrose Rehabilitation Hospital, University of Alberta, Edmonton, AB, Canada, [3] Department of Physical Medicine and Rehabilitation, Glenrose Rehabilitation Hospital, University of Alberta, Edmonton, AB, Canada, [4] Department of Pediatrics, University of Alberta, Edmonton, AB, Canada, [5] Department of Physical Medicine and Rehabilitation, University of Hong Kong-Shenzhen Hospital, Shenzhen, China

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Britt Nakstad,
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Cincinnati Children's Hospital Medical Center, United States

****Correspondence:***
Po-Yin Cheung
poyin@ualberta.ca

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Background: Comprehensive multidisciplinary assessment of neurodevelopmental outcomes of high-risk neonates may have significant challenges in low- and middle-income countries, in addition to socio-cultural barriers. We aimed to compare the time to diagnosis of neurodevelopmental impairment (NDI) and cerebral palsy (CP) in preterm neonates (<29 weeks) at a multidisciplinary assessment and care (MDAC) clinic with that of a conventional high-risk infant follow-up clinic in China.

Methods: All eligible surviving very preterm neonates born at <29 weeks gestation at the University of Hong Kong–Shenzhen Hospital between January 2015 and December 2019 were followed up in conventional (2015–2017) and MDAC (2018–2020) clinics up to 2 years corrected age with clinical demographic information collected in a prospective database. The MDAC team used standardized developmental assessments. The rates and timing of diagnosing NDI and CP in two epochs were compared.

Results: The rates of NDI and CP were not different in two epochs [NDI: 12 (50%) vs. 12 (41%); CP: 3 (12%) vs. 2 (7%) of 24 and 29 surviving infants assessed in conventional and MDAC clinics, respectively]. Infants in the MDAC clinic were diagnosed with NDI and CP earlier than those in the pre-MDAC epoch (6 vs. 14 months corrected age, respectively, $P < 0.05$).

Conclusion: High-risk preterm neonates can be followed more effectively in a family-centered, child-friendly multidisciplinary clinic, leading to an earlier diagnosis of NDI and CP. Early counseling and interventions could be implemented accordingly.

Keywords: prematurity, cerebral palsy, neurodevelopmental impairment (NDI), multidisciplinary (care or team), early diagnosis, neurodevelopment

INTRODUCTION

Although the survival of very preterm infants continues to improve, extremely preterm birth remains a leading cause of neonatal death, short-term morbidity, and neurodevelopmental sequelae in early childhood (1). Among the neurodevelopmental sequelae during early childhood, neurodevelopmental impairment (NDI) is a composite outcome that includes significant motor, cognitive, and neurosensory impairments (2). Cerebral palsy (CP) is a group of permanent disorders of the development of movement and posture, causing activity limitation that is attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (3). In a National Institute of Child Health and Human Development study of extremely preterm infants (≤27 weeks gestation) between 2011 and 2015, 12% had CP and 16–34% had moderate-to-severe NDI between 18 and 26 months adjusted age (4). It was estimated that 3.5–14.9% of extremely preterm infants developed severe NDI in the Canadian Neonatal Follow-up Network (2). In China, there is limited information or large cohort studies regarding the neurodevelopmental outcome in extremely preterm infants.

A study from the Global low- and middle-income countries CP register recruited 2,664 children from Bangladesh, Nepal, Indonesia, and Ghana between January 2015 and May 2019 and showed that the median age of diagnosing CP was 3 years (5). In Vietnam, using a surveillance system modeled on the Pediatric Active Enhanced Disease Surveillance system in Australia, CP was diagnosed at a mean age of 1 year and 8 months (6). In China, CP was usually diagnosed at 1–2 years of age (7). However, two recent studies showed that early diagnosis of CP in the first year of life in high-risk infant follow-up clinics is both feasible and practical (8, 9). Further, many infants with NDI and CP respond well to interventions in early childhood when brain plasticity is at its greatest (10). Therefore, early diagnosis of NDI and CP could be crucial to influence the outcomes of these children and their families. Based on moderate-quality evidence, Novak et al. (11) advocated that the diagnosis of CP can and should be made as soon as possible so that (1) the infant can receive diagnostic-specific early intervention and surveillance to optimize neuroplasticity and prevent complications and (2) the parents can receive psychological and financial support. From the family-centered care perspective, most parents of children with CP want earlier diagnosis and do not want information withheld. They value honest and accurate information and research-driven diagnosis and treatment (12).

We aimed to evaluate the feasibility of implementing an "arena assessment" model by a multidisciplinary team and its timing in the diagnosis of CP and NDI in infants <29 weeks gestation in Shenzhen, China. Maitre et al. suggested that the implementation of this model could result in earlier detection of CP (9). We therefore hypothesized that the implementation of the multidisciplinary assessment and care (MDAC) clinic would lead to an earlier diagnosis of NDI and CP, when compared to the conventional follow-up program of high-risk preterm infants.

METHODS

This retrospective observational study was approved by the University of Hong Kong–Shenzhen Hospital Institutional Ethics Committee [#(2021)058]. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

In Shenzhen, there are ∼200,000 births annually in a population of 20 million. There are ∼300 neonates admitted to the neonatal intensive care unit (NICU) at University of Hong Kong–Shenzhen Hospital annually. Our NICU provided family-centered care since 2013. Clinical and demographic information during hospital stay was collected in a prospective database, and the diagnosis of neonatal morbidities including neonatal sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity followed that of international definitions (13). The data from all preterm infants, who were born at <29 weeks gestation from January 2015 to December 2019, survived and discharged from the NICU, and seen at the follow-up clinic in 2015–2020, were included in the study.

High-Risk Infant Follow-Up Clinic in 2015–2017 (Pre-MDAC Epoch)

The high-risk infant follow-up clinic at the University of Hong Kong–Shenzhen Hospital routinely followed all neonates who were born in this hospital with medical complexity in the perinatal period including but not limited to prematurity, low birth weight (<2,500 g), small for gestational age, asphyxia, neonatal encephalopathy, neonatal stroke, congenital heart defects, or other anomalies. It was held twice weekly. Many children with less common risk factors for CP also received care in this clinic. The national guidelines recommended the follow-up of high-risk neonates at 6 weeks after discharge from the NICU and every 3–6 months thereafter. All visits included medical and neurological exams, needs assessment by neonatologists, and standardized testing by certified nurses (the Ages and Stages Questionnaire, v.3, ASQ-3; Zhuhai Ocean Educational Science & Technology Co., Ltd, Zhuhai, China, at 12 and 18 months). After assessment, patients with special needs are referred to subspecialty programs (audiology, ophthalmology, CP, and physical medicine) as appropriate or offered a follow-up appointment. There was no specific early CP diagnostic program.

MDAC Clinic in 2018–2020 (MDAC Epoch)

In 2018, the follow-up of high-risk neonates for early diagnosis of CP was developed based on the model of the Nationwide Children's Hospital (8) and Novak et al. (11). An MDAC clinic that focused on following those preterm infants born at <29 weeks gestation was established, in addition to the visit at the high-risk infant follow-up clinic. The patient load at the MDAC clinic was lower than that of the high-risk infant follow-up clinic where a large population of high-risk infants were routinely monitored. This MDAC clinic was held monthly. The multidisciplinary team consisted of neonatologists;

nursing specialists; and physical, occupational, and speech therapists. The team received intensive training by international specialists including developmental pediatricians, physiatrists, and therapists experienced in the assessment and care of neonates at risk for NDI and CP through regular workshops and clinical teachings. In this provider-organized MDAC clinic, eligible infants were seen at 6, 12, 18, and 24 months adjusted age.

Clinical information during hospital stay was documented by nursing specialists from the MDAC team. Social media (WeChat) was used to maintain contact with parents after discharge and understand the concerns and needs of families. Nursing specialists interviewed parents 1 day in advance of the MDAC clinic to record the progress of their child, including (1) general conditions such as seizures, feeding, sleep, and bladder and bowel habits, (2) results of vision and hearing tests, (3) the administration of ASQ-3 at 12–18 months, and (4) other parental concerns.

Following the guidelines of early diagnosis of CP (8), a unique model of "arena assessment" was implemented in this MDAC clinic. All team members attended a pre-assessment case conference to be familiar with every case based on up-to-date clinical information from nursing specialists. Each infant was examined by one team member with other members observing the examination in close proximity. The examiner completed and scored the Hammersmith Infant Neurological Examination (HINE) and the Alberta Infant Motor Scale (AIMS). The HINE is an easily performed, relatively brief, standardized, and scorable clinical neurological examination for infants between 2 and 24 months of age. HINE is accessible to all clinicians, with good inter-observer reliability even in less experienced staff. The use of the HINE optimality score and cut-off scores provides prognostic information on the severity of motor outcome. The HINE can further help to identify those infants needing specific rehabilitation programs (14). The AIMS is a unidimensional scale that aims to assess gross motor development of children aged up to 18 months by observing the spontaneous repertoire of children's skills detected through 58 items grouped under four postures: prone (21 items), supine (9 items), sitting (12 items), and standing (16 items) (15). Neonatal cranial ultrasonography, MRI brain, and ASQ-3 questionnaire were reviewed. Intraventricular hemorrhage was graded using the Papile classification (16). We used the classification system by Himmelmann et al. to categorize MRI findings (17). Infants were classified and diagnosed as having normal motor development, delayed motor development, high-risk of CP, CP, and NDI at the time of clinic attendance based upon the above assessments. Delayed motor development in preterm infants was defined by the mean value for the AIMS below 10th percentiles at 4 months and below 5th percentiles at 8 months (18). The HINE was completed using the standard proforma and scored from 0 to 78. An HINE score <73 (at 6, 9, or 12 months adjusted age) was considered at high risk of CP (11), whereas a score <59 and <65 at 6 and 12 months adjusted age, respectively, indicates CP (19). NDI was defined as one of neuromotor, neurocognitive, and neurosensory impairments at 12–18 months adjusted age. Neuromotor impairment included CP, AIMS <10th percentiles at 4 months, <5th percentiles at 8 months, an HINE score <59 at 6 months or <65 at 12 months adjusted age, or ASQ-3 scores in both gross and fine motor domains at the monitoring zone, or one that was below the cut-off threshold. Neurocognitive impairment was defined as ASQ-3 scores with ≥ 2 domains including communication, problem solving, and personal–social, were within the monitoring zone, or ≥ 1 domain below cut-off threshold (20). Neurosensory impairment included visual or hearing impairment requiring corrective measures. The category of NDI was determined by the most severe impairment in any domain. At the post-clinic conference, the MDAC team discussed and adjudicated the infants' neurodevelopmental state based on physical findings, ASQ-3, HINE and AIMS scores, and neuroimaging. As the team lead, the neonatologist then had a family-centered conference with the parents, discussed the findings, and provided anticipatory counseling and a care plan. Referrals were made for infants at high risk of CP or with CP to the department of physical medicine and rehabilitation for early interventions and therapy as appropriate. Infants who were diagnosed with NDI due to vision or hearing impairment were referred to the ophthalmology or otolaryngology departments for further management.

Statistical Analysis

All analyses were conducted by using IBM Statistical Product and Service Solutions software Version 24 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the mean $\pm$ standard deviation and median with interquartile ranges (IQRs) for parametric and non-parametric distributions, respectively. The variables of two cohorts (pre-MDAC and MDAC epochs) were compared as well as those of infants diagnosed to have NDI and CP in the respective epoch. The parametric (Student's t) or non-parametric (Mann–Whitney U) tests were used to analyze variables accordingly. Comparisons of categorical variables were performed using the Pearson chi-square test or Fisher exact test. $P < 0.05$ was considered as statistically significant. Infants lost to follow-up in the study were not included in the analyses of the outcome variables.

RESULTS

From January 2015 to December 2019, 708 preterm neonates were admitted to our NICU with 73 (10%) born at <29 weeks' gestation. Thirteen (18%) of 73 neonates died during hospitalization. Among the 60 survivors, 49 (82%) had bronchopulmonary dysplasia, 28 (47%) had retinopathy of prematurity, 8 (13%) had severe necrotizing enterocolitis (stages II and III of Bell's classification), and 13 (22%) had major intraventricular hemorrhage (grades 3 and 4 of Papile staging). **Table 1** shows the socio-demographic and perinatal–neonatal characteristics of all infants in the follow-up clinics. Chorioamnionitis, small for gestational age, longer hospital stay, prolonged invasive ventilation, and more frequent packed red blood cell transfusions were common among those with NDI compared with those without NDI ($P < 0.05$). Gestational age, birth weight, sex, delivery mode, Apgar score at 5 min of life, maternal ages, premature rupture of membrane, gestational diabetes mellitus, gestational hypertension,

TABLE 1 | Socio-demographic and perinatal-neonatal characteristics between neurodevelopmental impairment (NDI) and non-NDI groups.

Variables	Non-NDI ($n = 29$)	NDI ($n = 24$)	*P*
Gestational age (weeks)	27.4 (26.6–28.1)	27.8 (26.4–28.2)	0.865
Birth weight (grams)	1,000 (920–1,105)	870 (735–1,100)	0.168
Male gender	14 (48%)	15 (63%)	0.300
Vaginal delivery	18 (62%)	13 (54%)	0.561
Apgar score at 5 min	8 (7–9)	8 (7–8)	0.531
Maternal age (years)	32 ± 4	34 ± 4	0.208
Premature rupture of membrane	3 (10%)	7 (29%)	0.081
Gestational diabetes mellitus	6 (21%)	3 (13%)	0.487
Gestational hypertension	2 (7%)	3 (13%)	0.649
Antenatal steroids	26 (90%)	22 (92%)	1.000
Magnesium sulfate	22 (76%)	13 (54%)	0.097
Maternal chorioamnionitis	3 (10%)	8 (33%)	**0.040**
SGA (birth weight <10th percentile)	0 (0%)	4 (17%)	**0.036**
Hospital length of stay (days)	76 (58–95)	91 (72–116)	**0.043**
Surfactant therapy (%)	15 (52%)	14 (58%)	0.630
Lowest temperature in 0–12 h (°C)	36.5 (35.8–36.7)	36.4 (36.0–36.7)	0.525
Duration of invasive ventilation (days)	0.04 (0–7)	6.75 (0.35–14.9	**0.028**
Duration of non-invasive ventilation (days)	51 ± 19	54 ± 23	0.568
Number of packed RBC transfusions	1 (0–3)	3 (2–4)	**0.016**
Neonatal sepsis	7 (24%)	7 (29%)	0.679
Bronchopulmonary dysplasia	25 (86%)	19 (79%)	0.715
Intraventricular hemorrhage (≥grade3)	5 (17%)	7 (29%)	0.302
Necrotic enterocolitis (≥stage II)	3 (10%)	5 (21%)	0.444
Retinopathy of prematurity	13 (45%)	15 (63%)	0.200
Discharged on home oxygen	1 (3%)	5 (21%)	0.080
Discharge weight (grams)	2,725 (2,260–2,995)	2,700 (2,390–3,363)	0.514
Corrected age of MRI (weeks)	38.5 (36.4–41.1)	39.7 (37.4–42.4)	0.192
Abnormal brain MRI	6/26 (23%)	7/22 (32%)	0.497
Periventricular leukomalacia	1 (3%)	4 (17%)	0.164

SGA, small gestational age; RBC, red blood cell; MRI, magnetic resonance imaging; The bold values were used to indicate significance with P-values <0.05.

antenatal steroids, magnesium sulfate, surfactant therapy, lowest temperature within 12 h after birth, surfactant therapy, non-invasive ventilation days, neonatal sepsis, bronchopulmonary dysplasia, major intraventricular hemorrhage, severe necrotizing enterocolitis, all types of retinopathy of prematurity, discharged on home oxygen, discharged weight, corrected age of MRI, abnormal MRI findings, and periventricular leukomalacia were not different between infants with NDI and without NDI. Magnetic resonance imaging was performed in 48 (91%) infants, of whom 13 (27%) had abnormal brain findings including periventricular leukomalacia ($n = 5$) (**Table 1**).

In the pre-MDAC epoch (2015–2017), 6 (20%) of 30 surviving infants lost to follow-up, whereas, 1 (3%) of 30 survivors lost to follow-up in the MDAC epoch (2018–2020) ($P > 0.05$). The remaining 53 infants were born at 27.3 ± 1.3 weeks gestation with birth weight 971 ± 215 g and 29 (55%) of male sex. Twenty-four (45%) infants had NDI. Five (9%) infants were diagnosed with CP, with 2 (4%) infants <12 months adjusted age diagnosed as at high risk for CP. Severe visual and hearing impairments were diagnosed in 4 (8%) and 2 (4%) surviving infants, respectively (**Table 2**).

During the two epochs, ASQ-3 questionnaires were administered to 49 (92%) infants (**Table 3**) at the mean-adjusted age of 13.5 and 14.4 months for those infants without and with NDI, respectively. There were three un-validated completion of ASQ-3 questionnaires and one parental refusal in pre-MDAC and MDAC epochs, respectively. It was common for the scores of fine motor, personal–social, problem-solving, and communication domains to be below cut-off threshold among those infants with NDI, when compared with those without NDI ($P < 0.05$). Regarding the scores below the cut-off threshold of the gross motor domain, there was no difference between NDI and non-NDI infants ($P = 0.072$).

During the MDAC epoch, HINE and AIMS were implemented in MDAC clinic by the team. The mean adjusted age at the diagnosis of NDI and CP during the MDAC epoch was significantly lower than that during the pre-MDAC epoch [6 (5–12) vs. 14 (11–18) months, respectively, $P = 0.02$] (**Table 4**). There were no significant differences regarding demographic, clinical and neuroimaging findings, and main short-term morbidity between surviving infants in the pre-MDAC and MDAC epochs, although infants assessed in the MDAC epoch

TABLE 2 | Neurodevelopmental outcomes during the pre-MDAC (2015–2017) and MDAC (2018–2020) epochs.

	Pre-MDAC (n = 24)	MDAC (n = 29)
Total neurodevelopmental impairment (%)	12 (50%)	12 (41%)
Mild neurodevelopmental impairment (%)	5 (20%)	9 (32%)
Moderate to severe neurodevelopmental impairment (%)	7 (29%)	3 (10%)
Cerebral palsy (%)	3 (12%)	2 (7%)
High-risk of cerebral palsy (%)	—	2 (7%)
Visual impairment (%)	3 (12%)	1 (4%)
Hearing impairment (%)	1 (4%)	1 (4%)

All P > 0.05.

Mild neurodevelopmental impairment: one of neuromotor impairment (GMFCS 2 or AIMS < 10th percentile at 4 month, <5th percentile at 8 month or HINE <59 at 6 month, <65 at 12 month corrected age or both gross and fine motor domains of ASO-3 in monitoring zone, or one is below cut-off), neurocognitive impairment (≥2 domains pf ASQ-3 including communication, problem solving and personal-social, scores in monitoring zone, or one of domains below cut-off) or neurosensory impairment (visual or hearing deficits not requiring corrective measures).

Moderate to severe neurodevelopmental impairment: a composite of neuromotor and neurocognitive and/or neurosensory impairment (GMFCS 3-5, or HINE < 40 or both gross and fine motor domains of ASO-3 are below cut-off and ≥2 domains including communication, problem solving and personal-social below cut-off; and/or visual or hearing deficits requiring corrective measures).

High-risk of cerebral palsy: HINE score <73 at 6, 9, or 12 months adjusted age, respectively.

TABLE 3 | Results of Ages and Stages Questionnaire (v.3) assessment in neurodevelopmental impairment (NDI) and non-NDI groups.

Variables	Non-NDI (n = 28)	NDI (n = 21)	P
Corrected age (month)	13.5 ± 7.5	14.4 ± 4.9	0.202
Gross motor below cut-off	0 (0%)	3 (14.3%)	0.072
Gross motor monitoring zone	2 (7.1%)	11 (52.4%)	**0.001**
Fine motor below cut-off	0 (0%)	4 (19.0%)	**0.028**
Fine motor monitoring zone	1 (3.6%)	4 (19.0%)	0.150
Communication below cut-off	0 (0%)	5 (23.8%)	**0.011**
Communication monitoring zone	1 (3.6%)	5 (23.8%)	0.072
Problem solving below cut-off	0 (0%)	4 (19.0%)	**0.028**
Problem solving monitoring zone	0 (0%)	2 (9.5%)	0.179
Personal-social below cut-off	0 (0%)	4 (19.0%)	**0.028**
Personal-social monitoring zone	1 (3.6%)	4 (19.0%)	0.150

There was no validated data in Ages and Stages Questionnaire (v.3) of one child and 3 children in non-NDI and NDI groups, respectively. The bold values were used to indicate significance with P-values <0.05.

had a higher discharge weight ($P = 0.045$) (**Table 4**). The infants of the pre-MDAC epoch and a lower score in communication domain ($P < 0.001$) than infants assessed in the MDAC epoch (**Table 4**).

DISCUSSION

This is the first report describing the implementation of early CP and NDI diagnosis using a family-centered MDAC clinic in a Chinese setting. The incidence of moderate to severe NDI was 19% in this study, compared to 16–32% reported in a National Institute of Child Health and Human Development study (4). The incidence of severe NDI in survivors between 18 and 26 months adjusted age ranged from 3.5 to 14.9% (n = 2187) (2). A Swedish study incidence of severe NDI was 11% at 2.5 years of age for their more immature cohort born at <27 weeks of gestation (21). The rate of CP (9%) in this study was lower than that observed by Adams-Chapman et al. (vs. 12%), whereas that of severe visual impairment (8%) was higher and severe hearing impairment (4%) was (vs. 1 and 3%, respectively) (4). We believe that the difference could be related to the variation in definitions, reporting mechanisms, cohort characteristics and corrected ages at the time of assessment and diagnosis.

Epidemiological studies have shown that the origins of most CP are prior to labor.

Maternal chorioamnionitis is associated with an increased risk of CP in term infants (21). Among a case-control study reported a strong association between maternal chorioamnionitis and CP (odds ratio 4.1, 95% confidence intervals 1.6–10.1) (22). Other risk factors include prematurity and small for gestational age (23). Mechanical ventilation has been associated with increased risk of CP (24). Recent studies on white matter microstructure in extremely preterm infants (gestational age <27 weeks) found that the number of days on mechanical ventilation was an independent contributor to diffuse white matter injury, especially in the right external capsule (25), the occipital periventricular zone, and the centrum semiovale (26). Red blood cell transfusion has a negative impact on survival in extremely low-birth- weight infants. The number of transfusions affects later neurodevelopment (27). We observed similar findings in the current study with higher incidence of maternal chorioamnionitis, small for gestational age, packed cell transfusion, and longer days of mechanical ventilation and hospital stay in the NDI group, when compared to those variables of non-NDI group (**Table 1**).

The attendance rate at the MDAC Clinic (97%) was higher than the pre-MDAC clinic (81%) but did not reach statistical significance, probably due to our small sample. Some clinicians had different comfort levels with giving the diagnosis of high-risk for CP or CP in our new MDAC program. Acquiring experience and establishing confidence in administering AIMS and HINE was at times difficult. For all these reasons, a team-based system with mutual support was established so that providers could always discuss and rely on a more advanced or experienced observer for consultative assistance. A regular case review once a quarter and workshops twice per year were held with the clinical experts in neonatal follow-up and physical medicine and rehabilitation (MJW) for quality assurance. For diagnosis, if the clinician did not feel comfortable or assessed that the family was not ready (emotional state, lack of support system, other parent not present, child acutely ill, or crying at visit) to receive a diagnosis, parents were counseled regarding delayed neurodevelopment and reassessment was arranged within 1–3 months to ensure early communication

TABLE 4 | Demographic characteristics, main morbidity, and Ages and Stages Questionnaire (v.3) (ASQ-3) scores of infants with neurodevelopmental impairment during pre-MDAC (2015–2017) and MDAC (2018–2020) epochs.

Variables	Pre-MDAC (*n* = 12)	MDAC (*n* = 12)	*P*
Gestational age (weeks)	28.0 (24.9–28.3)	27.1 (26.4–28.3)	0.887
Birth weight (grams)	880 (680–1,100)	850 (745–1,100)	0.843
Male gender	6 (50%)	9 (75%)	0.400
Vaginal delivery	7 (58%)	6 (50%)	0.682
Apgar score (5 min)	8 (7–8)	8 (8–9)	0.128
Maternal age (years)	33 ± 4	34 ± 4	0.389
Premature rupture of membrane	2 (17%)	5 (42%)	0.371
Gestational diabetes mellitus	1 (8%)	2 (17%)	1.000
Gestational hypertension	2 (17%)	1 (8%)	1.000
Antenatal steroids	11 (92%)	11 (92%)	1.000
Magnesium sulfate	5 (42%)	8 (67%)	0.219
Chorioamnionitis	3 (25%)	5 (42%)	0.667
SGA (birth weight <10th percentile)	2 (17%)	2 (17%)	1.000
Hospital length of stay (days)	104 ± 43	99 ± 31	0.912
Surfactant therapy (%)	8 (67%)	6 (50%)	0.408
Lowest temperature in 0–12 h (°C)	36.3 (35.5–36.6)	36.4 (36.3–36.8)	0.198
Duration of invasive ventilation (days)	8 (0–29)	7 (0.8–11)	0.799
Duration of non-invasive ventilation (days)	49 ± 15	60 ± 29	0.224
Number of packed RBC transfusions	4 (2–4)	3 (1–4)	0.347
Neonatal sepsis	5 (42%)	2 (17%)	0.371
Bronchopulmonary dysplasia	10 (83%)	9 (75%)	1.000
Intraventricular hemorrhage (≥grade3)	4 (33%)	7 (58%)	0.219
Necrotic enterocolitis of newborn (≥stage II)	3 (25%)	2 (17%)	1.000
Retinopathy of prematurity	9 (75%)	6 (50%)	0.400
Discharged on home oxygen	2 (17%)	3 (25%)	1.000
Discharge weight (grams)	2657 ± 382	3141 ± 741	**0.045**
Corrected age of MRI (weeks)	39 (37–42)	41 (38-42)	0.821
Abnormal brain MRI	4/10 (40%)	3/12 (25%)	0.652
Time of NDI and CP diagnosis (months)	14 (11–18)	6 (5–12)	**0.020**
ASQ-3 [*n* (%)]	10 (83%)	11 (92%)	1.000
Corrected age of ASQ-3 (months)	17.0 (11.3–22.5)	13.5 (11.2–17.1)	0.195
ASQ-3: Gross motor	29.2 ± 19.8	33.8 ± 16.4	0.543
ASQ-3: Fine motor	47.5 (20.0–50.0)	45.0 (35.0–57.5)	0.378
ASQ-3: Problem solving	30.0 (20.0–50.0)	40.0 (35.0–50.0)	0.242
ASQ-3: Personal-social	30.0 (12.5–40.0)	40.0 (25.0–50.0)	0.101
ASQ-3: Communication	24.2 ± 11.6	48.8 ± 10.1	**<0.001**
Hammersmith infant neurological examination score	—	48.5 ± 10	
Alberta infant motor scale score	—	15 (11–19)	

SGA, small gestational age; RBC, red blood cell; MRI, magnetic resonance imaging. The bold values were used to indicate significance with P-values <0.05.

of diagnosis, initiate early intervention, and parental support and counseling.

The guidelines by Novak et al. recommend that all high-risk infants should have MRI brain, HINE and AIMS performed at >5 months' corrected age to allow for the early diagnosis of CP (12). All infants, who did not have MRI brain at term corrected age, had at least three cranial ultrasound examinations during the stay in our NICU. Cranial ultrasound examinations have been shown to have a similar specificity to MRI for the diagnosis of CP but are less sensitive at detecting white matter changes at term (28). Cognitive impairment is significantly correlated with birth-weight and gestation age (29). Cognitive impairment is commonly measured using the cognitive scale or mental developmental index of the Bayley Scales of Infant Development or cognitive domains of ASQ-3. The American Academy of Pediatrics recommended the use of a parent-reported developmental screening tool, the ASQ-3, which had 75% sensitivity and 81% specificity when compared to the Bayley Scale of Infant Development-II (30). The ASQ-3 was performed in 92% of infants in this study (**Table 3**). In this study, low cognitive functions were significantly associated with positive ASQ-3 results in communication, problem solving and personal-social skills at 14 months corrected age, but not with gross motor skills. The correlation between communication and gross motor domains was the lowest, while the correlation between communication and problem solving was the highest, which is similar to the domain correlations reported previously by Agarwal et al. (31). The earliest sign of NDI is most likely manifested by motor impairment in the first year of life, in the form of CP or suspected CP, as language developmental abnormality may not be evident, except for feeding difficulties. Postnatal under-nutrition and faltering growth are common and associated with adverse cortical development in the neonatal period (32) and long-term neurodevelopmental outcomes (33). In a group of 613 babies born <33 weeks' gestational age, assessed at 18 months' corrected age, Belfort et al. found that every-one z-score improvement in weight gain and body mass index between 1 week of age and term-corrected age was associated with an increase in Bayley II mental developmental indices of 2.4 and 1.7 points and psychomotor developmental indices of 2.7 and 2.5 points, respectively (34). Interestingly, we found that significantly higher body weight at discharge in those infants with NDI during the MDAC epoch, when compared with that during the pre-MDAC epoch (**Table 4**). Further, these infants of the pre-MDAC epoch had a lower cut-off score of ASQ-Communication ($P < 0.001$) but not with other domains, which was similar to that in the study by Belfort et al. (35).

Compared with that during the pre-MDAC epoch, infants followed up in the MDAC program had CP diagnosed earlier (mean age 6 months) with mean cut-off of HINE scores of 48.5 ± 10 and mean AIMS scores of 15 (11–19) (<10th percentile). The age at diagnosis of CP in pre-MDAC epoch was 14 (range 11–18) months, which was similar to that of some low- and middle-income countries (5–7). The inclusion of a "precision" CP diagnosis program may contribute to the early diagnosis of CP during the MDAC epoch. Indeed, the identification of CP can be challenging in low- and middle-income countries because of the lack of resources and tools. However, HINE and AIMS are user-friendly. The AIMS is a unidimensional scale by observing the spontaneous repertoire of children's skills. Multilingual (English, Spanish, and French) versions of the HINE video and forms are available online at no cost (14), whereas other scales are costly or have lengthy certifications or proprietary forms. International guidelines for early detection of CP recommended using HINE, the most predictive neurological examination for CP, in the first year of life when the General Movements Assessment cannot be performed at 3–4 months of age or in countries where MRI is not available or affordable (11). Our findings and experience may benefit low- and middle-income countries.

There is evidence that the brain development and refinement of the motor system continue postnatally, driven by motor cortex activity (34). Early active movement and interventions are essential because infants who do not actively use their motor cortex risk lose cortical connections and dedicated function. CP-specific early intervention maximizes neuroplasticity and minimizes deleterious modifications to muscle and bone growth and development (36). Early diagnosis and early intervention are important to optimize infant motor and cognitive plasticity, prevent secondary complications, and enhance caregiver well-being. In this study, the decrease in age at the diagnosis of CP could be because of the creation of the MDAC clinic or because of the incorporation of the HINE and the AIMS (or both). However, one of the original aims for the creation of the MDAC clinic was to reduce the rate of loss to follow-up, which was not significant due to small sample size.

There are several limitations of this study. Firstly, this is a retrospective study of a small cohort of patients in a single center that precluded examining the effects of confounding variables. Secondly, we did not routinely use the General Movements Assessment prior to discharge from the NICU, which may help identify infants meeting the "infant-attributable risk" pathway of the international guidelines (11). Thirdly, we did not have the gold-standard developmental assessment in this age range, the Bayley Scale of Infant Development, because the translated and updated versions of the Bayley Scale of Infant Development are not available in China for various reasons including but not limited to logistics, cost, and copyright. Indeed, it is very challenging to establish an MDAC clinic in low- and middle-income countries. While it would be better to use these tests, we used assessment tools (HINE and AIMS) that are free and user-friendly.

In conclusion, in this pilot observational cohort study of critically ill preterm neonates with gestation age <29 weeks, a multidisciplinary "arena assessment" model with HINE, AIMS, ASQ-3, and MRI brain scan as objective measures is feasible and effective for an early diagnosis of NDI and CP in China. If other centers and studies confirm our findings and experience, early diagnosis of motor impairment may facilitate earlier identification of NDI in this population, especially in the low- and middle-income countries. A formal diagnosis of CP or high-risk of CP is essential for families to access necessary intervention and support in China.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Hong Kong-Shenzhen Hospital Institutional Ethics Committee [#(2021)058]. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

H-BH conceptualized and designed the study, drafted the initial manuscript, and revised the manuscript. P-YC conceptualized and designed the study, supervised clinical information/data collection, critically reviewed, and revised the manuscript. MW set up the MDAC clinic, implemented training of AIMS and HINE to staff, supervised clinical assessment, and revised the manuscript. Q-SZ conceptualized clinical information/data collection and critically reviewed the manuscript for important intellectual content. MH implemented HINE training and critically reviewed the manuscript for important intellectual content. C-BC set up the high-risk infants follow-up clinic and supervised clinical information/data collection. FL and X-QW were involved in the care and assessment of the follow-up patient, collected clinical information/data, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Prediction of Retinopathy of Prematurity Using the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity) Algorithm in a South African Population

Samantha Jane Kesting and Firdose Lambey Nakwa*

Department of Paediatrics, Division of Neonatology, Faculty of Health Sciences, School of Clinical Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa

Aim: This study aimed to assess the efficacy of the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity) screening algorithm in a South African population.

Methods: A retrospective record review included infants born between 1 January 2013 and 1 December 2014 who underwent ROP (retinopathy of prematurity) screening. Outcomes of ophthalmology examinations were compared to alarms triggered on WINROP after gestational age, date of birth, and weekly weights were entered. Sensitivity, specificity, positive predictive, and negative predictive values and mean time of alarm were calculated.

Results: Rates of ROP were 5.9% for all stages of ROP and 2.3% for severe ROP in the 220 infants included. Mean gestation age was 29.1 ± 1.3 weeks and mean birth weight 1,115.5 ± 201 g. WINROP triggered high-risk alarms in 70.5% of infants at a mean of 30.7 weeks of gestational age. Sensitivity for severe ROP was 100 and 76.9% for all stages of ROP. Specificity was low for both severe ROP and all stages of ROP at 30.2 and 30.0%, respectively.

Conclusion: Rates of ROP are low in this population. The high number of alarms with a low negative predictive value would reduce the number of screens by 29.5%. Alarms were triggered before scheduled screening, possibly helpful in planning discharges and follow-up visits.

Keywords: IGF-1, retinopathy, prematurity, WINROP, NICU, blindness

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Ashish KC,
Uppsala University, Sweden

Reviewed by:
Noa Ofek-shlomai,
Hadassah Medical Center, Israel
Anil Gangwe,
MGM Eye Institute, India

****Correspondence:***
Samantha Jane Kesting
Samantha.kesting@wits.ac.za

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INTRODUCTION

Retinopathy of prematurity (ROP) has been found to be the third leading cause of avoidable blindness worldwide (1). In developing countries where neonatal intensive care is still evolving, oxygen therapy is often liberally used and inadequately monitored, placing infants at risk of ROP (2). At the Chris Hani Baragwanath Academic Hospital, Mayet et al. found the mean birth weight of neonates with ROP to be 1,093.7 g, compared to those without ROP at 1,215.6 g. No severe ROP was found in infants above 1,250 g. Although ROP was found in 16.3% of infants, disease requiring treatment was found only in 1.6% (3).

The South African screening guideline recommends screening neonates born below 32 weeks of gestation, weighing <1,500 g at birth or with risk factors such as family history, cardiac arrest, multiple blood transfusions or exchange transfusions, and hypoxic ischemic encephalopathy. The examinations are to be conducted between 31 and 32 weeks of corrected gestational age or between 4 and 6 weeks of chronological age, whichever is later (4). At the Chris Hani Baragwanath Academic Hospital, studies have shown that gestational age is an unreliable factor to assess risk in our population due to infrequent first-trimester ultrasound scans and uncertain last menstrual periods. For this reason, the screening criteria are based on birth weight (3). A shortage of specialized ophthalmology services and screening programs resulted in only 19.2% of infants who fulfill the screening criteria being examined by an ophthalmologist in South Africa (5).

WINROP is a web-based computer program that works from a reference model calculated using logistic regression with expected values from the weights and IGF-1 levels of infants with no or mild ROP (6). Once the sex, gestational age at birth, and weekly weights have been entered, risk is indicated as red or green lamps indicating high or low risks, respectively. The timing of a high-risk alarm is also indicated in gestational age in weeks. The final ophthalmology examination is also inserted into the online database.

WINROP has been validated using retrospective cohort studies for the prediction of severe ROP in Europe, North America, South America, and Asia with sensitivities ranging from 84.7 to 100% (6–13). No data have been published regarding the efficacy of WINROP in an African population.

This study aimed to assess the efficacy of WINROP as a screening tool in predicting ROP in infants undergoing ROP screening at the Chris Hani Baragwanath Academic Hospital.

METHODS

A retrospective review of the records of patients who underwent ROP screening as per guidelines at the Chris Hani Baragwanath Academic Hospital was undertaken. Registration for WINROP was undertaken prior to commencement of the study with The Sahlgrenska Center for Pediatric Ophthalmology Research, allowing us access to the online program with a password-protected login. The study was approved by the University of the Witwatersrand Human Research Ethics Committee, clearance number M151123.

Weekly ROP screenings are performed by registrars in ophthalmology and referred to consultants as required. ROP was classified according to the International Classification of ROP (14). The ophthalmology reports of the routine ROP screenings were reviewed along with the patient records to obtain the required data. As only the inpatient records were available for review, only screenings done as an inpatient could be recorded. Not all patients had completed ROP screening by the time of discharge, and so the ROP diagnosis at the time of discharge was used for the study.

The gestational age, date of birth, weekly weights, and final ophthalmology screening results were entered into the online WINROP algorithm. Patient identifiers such as names and hospital numbers were recorded in a separate document to ensure confidentiality. The ETROP study (15) was the basis for the categorization in the study such as no ROP, mild ROP, and severe ROP as done in a previous evaluation of WINROP for uniformity (6).

Patient records were reviewed for infants born between 1 January 2013 and 31 December 2014 who qualified for ophthalmology ROP screening. The screening guidelines for ROP as per the Chris Hani Baragwanath Academic Hospital guidelines have the following inclusion criteria:

1. All infants with a birth weight of below 1,500 g
2. Infants with a birth weight of 1,500–2,000 g who received mechanical ventilation for more than 7 days
3. Infants with a birth weight of 1,500–2,000 g who received supplemental oxygen for more than 2 weeks
4. Infants with any birth weight who received supplemental oxygen for more than 6 weeks.

WINROP can be used reliably only for a gestational age at birth of 23 weeks + 0 days to 31 weeks + 6 days. For this reason, infants screened by the ophthalmology unit as per the guidelines listed above, but with a gestation >32 weeks were excluded. Due to the majority of the gestational ages in our study being calculated by examination with the New Ballard Score (16), which estimates gestation to full weeks, those at 32 weeks were included as 31 weeks + 6 days. Neonates that were noted to have conditions leading to disproportionate weights such as hydrocephalus were excluded (**Figure 1**).

The only other published study recording the prevalence of ROP in this setting was a study by Mayet which was published in 2006 (3). Using the frequency from this study of 16.3% for any ROP, a required sample size of 207 was calculated, allowing a margin for error of 5%, and a total of 220 patients were included.

The outcomes of the ophthalmology clinical examinations were then compared to the alarms triggered on the system. Sensitivity and specificity, as well as positive predictive and negative predictive values, were calculated based on high-risk alarms and clinical findings of ROP. The mean time of alarm and average weight gain per week were also calculated. The average weight gain per week was calculated using the difference between subsequent average weights per gestational and chronological age.

RESULTS

The rates of ROP in our population were low for all stages of ROP at 5.9% and severe ROP at 2.3%. Two patients were treated with bevacizumab injections by the ophthalmology unit as inpatients (**Table 1**). A total of 144 (97.3%) were of the African race.

Abbreviations: ETROP, Early treatment for retinopathy of prematurity; ROP, Retinopathy of prematurity; WINROP, Weight, IGF-1, Neonatal Retinopathy of Prematurity.

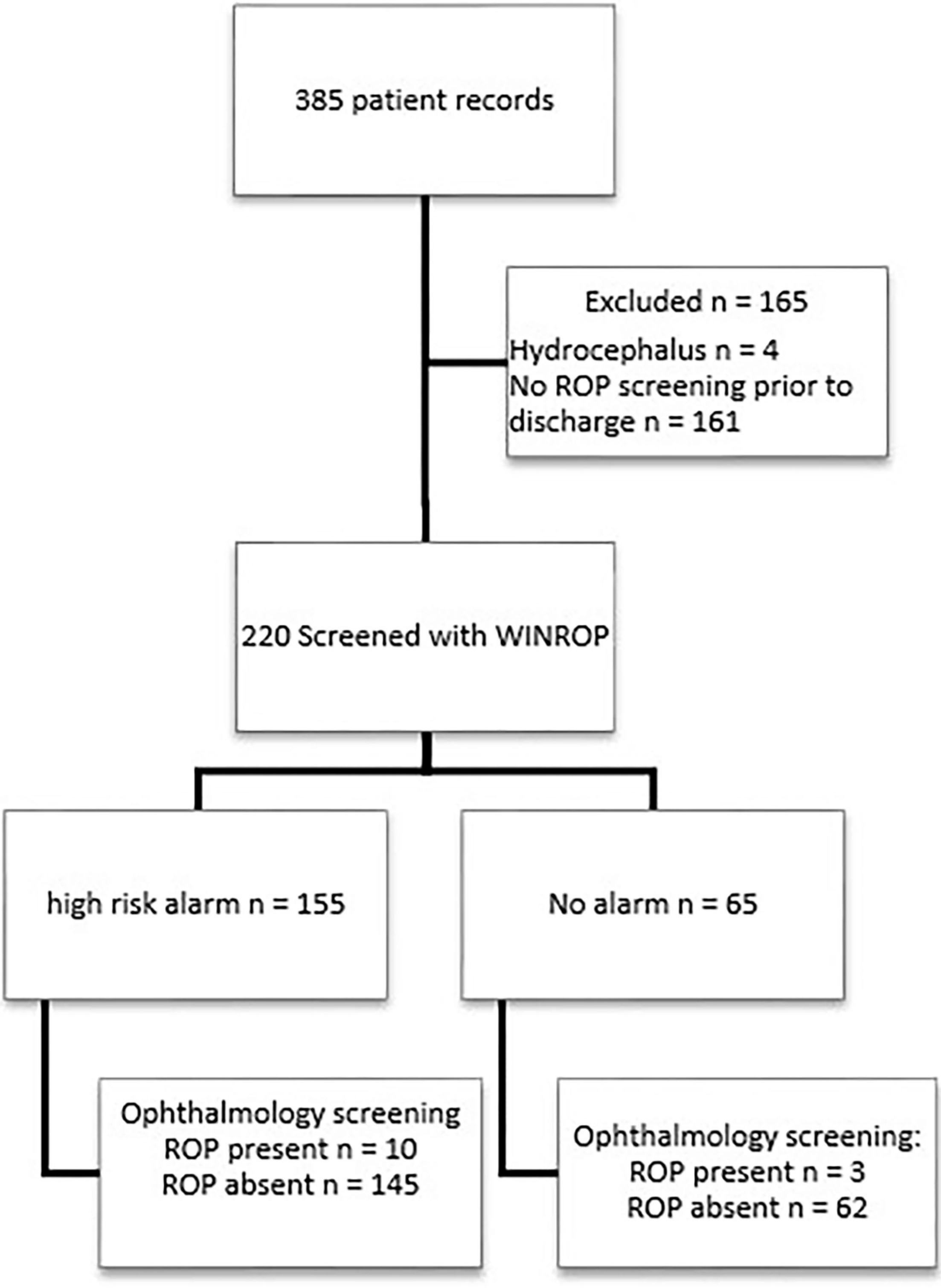

FIGURE 1 | Flow of participants.

TABLE 1 | Patient characteristics and rates of ROP.

Number of infants	220
Gestational age mean (weeks)	29.1 ± 1.3
Birth weight mean (grams)	1.115 ± 201
Male gender [*n* (%)]	108 (49.1%)
No ROP [*n* (%)]	207 (94.1%)
ROP mild [*n* (%)]	8 (3.6%)
ROP severe [*n* (%)]	5 (2.3%)
ROP treated as inpatient [*n* (%)]	2 (0.9%)

TABLE 2 | WINROP performance in predicting ROP.

	Severe ROP	All ROP
Sensitivity	100%	76.9%
Specificity	30.2%	30.0%
NPV	3.2%	6.5%
PPV	100%	95.4%
Positive likelihood ratio	1.4	1.1

The WINROP program triggered a high-risk alarm in 155 out of 220 infants (70.5%) at a mean of 30.7 ± 1.3 weeks of gestational age. Seventeen infants triggered an alarm at birth for being significantly small for gestational age, although none went on to develop any ROP (**Table 2**). All the severe-ROP patients triggered a high-risk alarm. Compared to the sensitivity for severe ROP (100%), the sensitivity for all stages of ROP was reduced to 76.9%. With the low specificity, the positive likelihood ratios were 1.1 for all stages of ROP and 1.4 for severe ROP.

DISCUSSION

The rates of ROP in our population were found to be low at 5.9% for all stages of ROP and 2.3% for severe ROP, when compared to other populations in the upper-middle-income countries (17). Despite the neonatal unit having far fewer oxygen blenders and less stringent oxygen saturation targets at the time, the rates of ROP were still low compared to other upper-middle-income countries with all stages of ROP at 16.3% and stage 3 of ROP at 2.5% (3). Another study in South Africa at Kalafong Provincial Tertiary Hospital by Delport et al. in 1999 (18) analyzed only the black infants screened and showed rates of 24.5% for all stages of ROP and 6.4% for stage 3 ROP. Other studies on ROP in South African populations have not commented on race for further comparison.

High-risk alarms were triggered by a large proportion of infants at the Chris Hani Baragwanath Academic Hospital (70%) considering the low rate of ROP (5.9%), resulting in a low negative predictive value. As a comparison, in other countries who have studied WINROP, Mexico had more alarms at 79.2% but also found severe ROP in 56.3% of their infants. In this population, ROP was found in larger, more mature infants. It was also disclosed that gestational age estimates, antenatal care, and oxygen monitoring were suboptimal (10).

The sensitivity of WINROP in our study was 100% for severe ROP but reduced for all stages of ROP at 76.9%. However, the positive likelihood ratios only indicate a minimal increase in the likelihood of disease with a high-risk alarm.

The high number of alarms appears to be related to our poor growth rates postnatally, which deviates from the algorithm used by WINROP. The average weight gain ranged from 0.66 to 12 g/day, which is far below the 15–17 g/kg/day recommended (19). Rooming facilities are limited in our setting, and expressed breast milk is not available in adequate volumes. Our donor breast milk bank is also limited and only available for a limited time to the smallest infants.

A study conducted in a multiracial London neonatal unit showed that black infants had lower levels of IGF-1 when compared to white patients. Along with the lower IGF-1 levels, they also had lower absolute postnatal weight gain. Despite these known risk factors, the black infants still needed less treatment for ROP than the white infants (20). The rates of severe ROP have also been found to be lower in infants of African descent in other studies in the USA, the United Kingdom, and Israel (21–24). This is suggested to be due to increased melanin, a known superoxide free radical in the retina. This would suggest that screening algorithms relying on growth and IGF-1 levels are population and race dependent, which may account for the differences in the efficacy of WINROP outside of Sweden, including in our study.

WINROP may assist in predicting those who are at highest risk of ROP requiring priority screening, although the low positive likelihood ratio only gives a minimal increase in the likelihood of disease. With such a high number of alarms, WINROP would only potentially reduce the numbers for screening by 30%. The alarm was triggered at a mean of 30.7 weeks of gestational age, which is before the routine screening by ophthalmology. This could perhaps assist in the planning of discharges and follow-up visits in infants discharged before the screening, as frequently happens in our hospital with a discharge weight of 1,650 g.

Rates of ROP were lower than the previous study in our population, which would influence the accuracy of the sample size calculation and therefore the power of the results. This was a prospective study and included all babies seen by ophthalmology for screening at birth during the period of July 2001 to December 2003 (3). It is likely that the reduction in the prevalence was due to the development of more stringent oxygen saturation protocols in the neonatal unit and the presence of more vital sign monitors and oxygen blenders than were available in 2003. These interventions are indeed not always present in a rural context, and so this would make it difficult to extrapolate to less-resourced units. In a survey of current oxygen management, screening criteria, and methods for treating ROP in sub-Saharan Africa, this unit is in a better-resourced position compared to the median of 3.5 oxygen measurement devices and 0 oxygen blenders and maximums of 70 and 50, respectively (25). These efforts in reducing the risk factors have resulted in a reduction in the rates of ROP in our population. However, due to resource constraints, infants below a weight of 1,000 g are not offered admission to the neonatal intensive care unit (NICU) and invasive ventilation, meaning the smallest premature infants are less likely to survive. The mean birth weights of infants from highly developed countries with severe ROP ranged from 737 to 763 g compared with from 903 to 1,527 g in less-developed countries (26).

As a retrospective record review of inpatient files, only the inpatient ROP screening examinations were captured. The final diagnosis or stage of ROP may have differed if the infants were referred or reviewed as outpatients to the ophthalmology department. With rotation of ophthalmology registrars through the department, there may be inconsistency in the screening examination. Gestational ages may be inaccurate as they are often based on last normal menstrual periods, symphysis pubis measurements, or postnatal New Ballard Scores performed by junior staff (16). The gestational age at birth is a critical part of the WINROP algorithm, influencing results.

CONCLUSION

Rates of ROP are low at the Chris Hani Baragwanath Academic Hospital. This may be due to the vast majority of patients being African, which is known to be a protective factor against ROP.

WINROP showed 100% sensitivity but a low specificity and low negative predictive value secondary to a large proportion of high-risk alarms. The likelihood of disease was only minimally increased with a high-risk alarm. It appears that the test would be of limited benefit in our population. The increased alarms were due to poor postnatal weight gain that deviated from the algorithm. The poor growth in our infants is multifactorial and requires further investigation.

Our study seems to confirm that IGF-1 levels and growth are population and race dependent, resulting in differences in the performance of WINROP compared to those in other parts of the world. This could form the basis of a future prospective study. A future prospective study would be useful at a district or rural hospital where ophthalmology review is logistically difficult or not available as some benefit may be offered by reducing the number of referrals required.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of the Witwatersrand Human Research Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SK and FN contributed to conception and design of the study and contributed to manuscript revision, read, and approved the submitted version. SK organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Ending Neonatal Deaths From Hypothermia in Sub-Saharan Africa: Call for Essential Technologies Tailored to the Context

Giorgia Brambilla Pisoni[1], Christine Gaulis[1], Silvan Suter[1], Michel A. Rochat[1], Solomzi Makohliso[1], Matthias Roth-Kleiner[2], Michiko Kyokan[3], Riccardo E. Pfister[3] and Klaus Schönenberger[1]*

[1] *École Polytechnique Fédérale de Lausanne, EssentialTech Centre, Lausanne, Switzerland,* [2] *Clinic of Neonatology, Department Women-Mother-Child, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland,* [3] *Neonatal and Paediatric Intensive Care Unit, University Hospitals of Geneva and Geneva University, Geneva, Switzerland*

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Edited by:
*Susan Coffin,
University of Pennsylvania,
United States*

Reviewed by:
*Sithembiso Velaphi,
University of the Witwatersrand,
South Africa
Gugu T. J. Kali,
Stellenbosch University, South Africa*

***Correspondence:**
*Giorgia Brambilla Pisoni
giorgia.brambillapisoni@gmail.com*

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Neonatal death represents a major burden in Sub-Saharan Africa (SSA), where the main conditions triggering mortality, such as prematurity, labor complications, infections, and respiratory distress syndrome, are frequently worsened by hypothermia, which dramatically scales up the risk of death. In SSA, the lack of awareness on the procedures to prevent hypothermia and the shortage of essential infant devices to treat it are hampering the reduction of neonatal deaths associated to hypothermia. Here, we offer a snapshot on the current available medical solutions to prevent and treat hypothermia in SSA, with a focus on Kenya. We aim to provide a picture that underlines the essential need for infant incubators in SSA. Specifically, given the inappropriateness of the incubators currently on the market, we point out the need for reinterpretation of research in the field, calling for technology-based solutions tailored to the SSA context, the need, and the end-user.

Keywords: Sub-Saharan Africa (SSA), newborn, mortality rate, hypothermia, incubators, low weight at birth, prematurity

INTRODUCTION

Among the 17 Sustainable Development Goals (SDGs) conceived in 2015 by the 2030 Agenda for Sustainable Development[1], SDG3 deals with ensuring health and promoting well-being for all, at all ages. In particular, SDG3.2 aims at reducing the mortality rate of children below 5 years of age (i.e., under-five; 25 deaths per 1,000 live births by 2030), including newborns (i.e., 1–28 days of age; 12 deaths per 1,000 live births by 2030)[2], An overall reduction of the under-five mortality has been achieved worldwide, especially in high-income countries (HICs), however, low- and middle-income countries (LIMCs) are still far in the process of meeting the mortality rate defined by SDG3.2 (1). Of note, in LMIC settings, the COVID-19 outbreak has strongly compromised the health scenario, therefore, a substantial rise in child deaths is expected in the upcoming years (2).

[1]https://sdgs.un.org/goals
[2]https://unstats.un.org/sdgs/report/2020/goal-03/

Sub-Saharan Africa (SSA)[3] is the region worldwide displaying the highest under-five and neonatal mortality rates (76 and 27 deaths per 1,000 live births in 2019, respectively) (3). SSA accounts for almost half (∼42%) of the global neonatal deaths occurring every year (3); in fact, of the global 2.45 million newborn deaths of 2019, roughly 1 million have died in SSA solely (4).

Prematurity (∼35%), asphyxia (∼24%), infections (∼23%), and congenital anomalies (∼11%) are considered the leading causes of neonatal mortality (5). In developing countries, and particularly in SSA, neonatal hypothermia strongly increases the risk of death (6). Neonatal hypothermia, defined by the WHO as the neonatal thermal state by which the body temperature falls below 36.5°C (7), is conventionally, classified into three main sub-groups: cold stress (36.4–36.0°C), moderate hypothermia (35.9–32.0°C), and severe hypothermia (<32.0°C) (7).

Despite almost never considered the cause of death *per se*, hypothermia highly increases the risk of neonatal mortality when concomitant with one of the aforementioned leading causes of death (6, 8). In SSA, newborns are at particularly high risk of hypothermia due to a mix of physiological features (i.e., high incidence of low-weight at birth and prematurity), cultural beliefs (i.e., delayed breastfeeding/skin-to-skin contact/drying and wrapping, late hospital admission, newborn bathing/oil massage right after birth), and socioeconomic factors (i.e., high prevalence of home deliveries, absence of skilled care at delivery and unavailability of medical devices, including for post-delivery transport, poverty, and out-of-pocket payments for health services). These factors merge with a critical health care condition of shortage in essential infrastructures (i.e., neonatal units and equipment) and a lack of awareness of the risks associated to hypothermia (i.e., absence of skilled personnel and insufficient or absent training for hypothermia prevention and treatment) (9–13).

Moreover, in the resource-depleted settings of SSA, neonatal death registries are often incomplete and inaccurate, live births under-reported, causes of death misclassified, and newborn body temperature often unmeasured (6, 8, 14). It comes with no surprise, hence, that the epidemiological prevalence of neonatal hypothermia is difficult to evaluate in these countries, with estimates ranging from 32 to 85% in hospital-born infants, and from 11 to 92% for home deliveries (6). Alongside, the prevalence of hypothermia in SSA hospitals spans from 8% within the first 12 h after birth to 85% in the case of hospital admission (13). In general, such broad intervals reflect a lack in the knowledge about the incidence and prevalence of hypothermia, both from a clinical and an epidemiological perspective (6). However, this gap in the knowledge should not lead to underestimate the burden of hypothermia, which is indeed a "silent epidemic" (10).

The first set of thermal care guidelines to prevent and treat hypothermia has been assembled by WHO in 1997 and referred to as the warm chain. The warm chain consists of 10 essential measures, which are: (i) warm delivery room, (ii) prompt newborn drying, (iii) skin-to-skin contact or Kangaroo Mother Care (KMC), (iv) prompt breastfeeding, (v) postponement of bath and weighing, (vi) appropriate clothing and bedding, (vii) promotion of mother-baby contact, (viii) warm transportation, (ix) warm resuscitation, and (x) awareness and adequate training (7). Despite these guidelines, neonatal hypothermia remains a major determinant of infant death in SSA countries. Indeed, some measures may be insufficient or unpractical in the SSA context (9–13).

In this article, we present a description of the current practices and tools to prevent and treat hypothermia, focusing on the medical devices available on the market. We also include a snapshot on conceptual and technological development of infant incubators throughout history. We focus on the SSA context for a comprehensive summary of thermal practices and equipment for neonates, with a particular focus on Kenya. Our aim is to uncover bottlenecks in technology-based thermal solutions to help reduce neonatal mortality. We propose a model to reinterpret the current body of evidence and foster a context- and end user-informed research in the field of essential technologies for newborns.

Search Strategy and Selection Criteria

We searched PubMed and MEDLINE for peer-reviewed articles published in English between 1997 [WHO definition of neonatal hypothermia, (7)] and 2021. An initial search (papers identified are {in brackets}) has been conducted using the following keywords: "newborn AND hypothermia" {3553}, "neonatal mortality AND hypothermia" {1030}, "neonatal hypothermia AND prevalence" {776}. Afterwards, inclusion criteria about the relevant context (i.e., "newborn AND hypothermia AND developing countries" {85}, "neonatal mortality AND hypothermia AND developing countries" {52}, "neonatal hypothermia AND prevalence AND developing countries" {39}, "neonatal hypothermia AND Sub-Saharan Africa" {109}) and the year of publication (1997–2021 range selected) have been included. Of these 285 papers identified, the relevant ones have been cited accordingly. Of note, we have not filtered the search for "infant incubators AND hypothermia" {91} and "infant warmers AND hypothermia" {82} for time or context. International reports from humanitarian organizations (i.e., UN, UNICEF, and WHO) have been included. Book chapters, demographic data, market news, and press articles on released technologies have also been thoroughly searched on the web and included as footnotes.

Patient and Public Involvement: no patient involved.

[3] All countries to the south of the Sahara desert: Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Togo, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

Description of the Nature of the Evidence Being Addressed and Rationale for the Proposed Hypothesis and Theory

Newborn Hypothermia: Prevention and Treatment

Clinical neonatal thermal care first relies on prevention of established hypothermia. Hypothermia prevention mostly appeals to the maintenance of an appropriate environmental temperature. In the WHO warm chain document of 1997 (7), the first recommendation focuses on warm delivery rooms. At birth, newborns are exposed to an environment at least 10°C colder than the in-utero (∼37.5°C) maternal body temperature. As such, the WHO recommends a room temperature at delivery of 26-28°C, in most contexts warmer than the indoor room temperature range (18–24°C) (15). The second preventive recommendation in the warm chain addresses prompt drying and warm wrapping of the newborn to primarily reduce evaporative heat losses, but also convection, conduction, and radiation (15). A systematic review has for instance shown that the use of plastic bags to wrap the newborn right after birth is associated to less hypothermia and higher temperature at admission, specifically in the case of low-birth-weight newborns (16). Of note however, only 4 of the 43 studies analyzed in this systematic review concerned LMIC settings (16).

The third recommendation focuses on the close warming contact between the mother and the infant (i.e., skin-to-skin contact or KMC, alongside breastfeeding). KMC was proposed

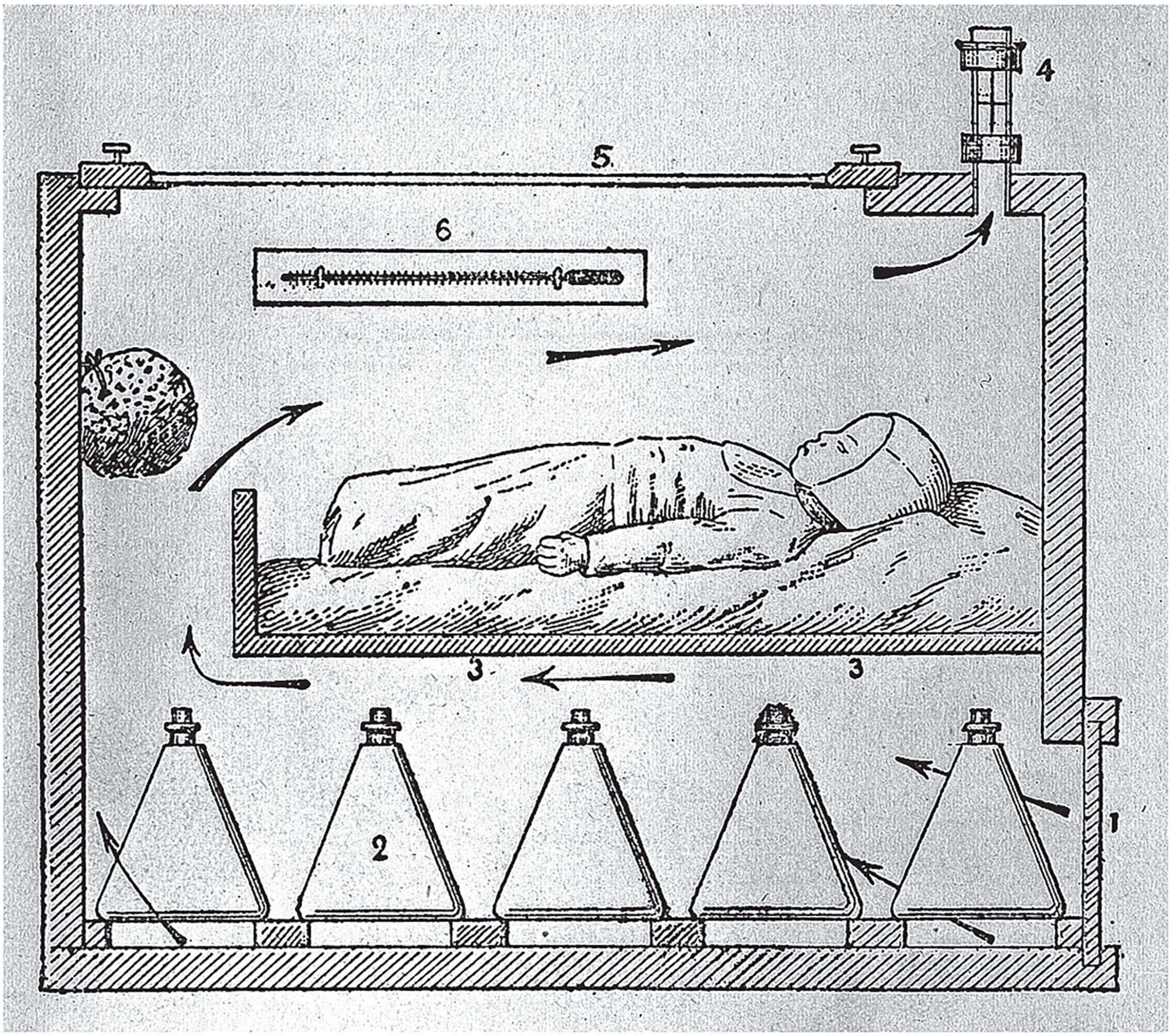

FIGURE 1 | Section of Tarnier's Incubator. Retrieved from: https://commons.wikimedia.org/wiki/File:Section_of_Tarnier%27s_incubator;_Budin,_The_Nursling,_1907_Wellcome_L0005632.jpg. Arrows indicate the air flow.

at first in 1978. It rapidly became an essential component within the standard newborn care program for infant thermal care and effective prevention of hypothermia (17). KMC consists in the uninterrupted skin-to-skin contact between the newborn and the mother's or caregiver's chest. Importantly, KMC application contributes at least to a 40% reduction in the neonatal mortality rate (18). KMC is especially recommended for clinically stable low-birth-weight and premature newborns (19–21). Of note, KMC has been shown to reduce the mortality of low-birth-weight newborns by 25% when initiated immediately after birth (22).

Despite this, however, the implementation of KMC remains slow in LMICs, mostly because of inadequate and poorly developed neonatal care units (i.e., lack of KMC-dedicated spaces, shortage of healthcare workers, beds and chairs, lack of privacy, cultural aspects, and overcrowding) (19–21).

When preventive measures are not applied or sufficient, clinical neonatal thermal care relies on treatment of hypothermia. For that, all WHO recommendations depend on the availability and good operation of technical devices for re-warming, such as incubators and radiant warmers (7).

Essential Technologies to Treat Hypothermia: Incubators and Warmers

Historical Development of Infant Incubators and Warmers

The first proof of existence of an incubator for premature newborns goes back to 1722, when the Italian physician Giuseppe Liceti put together a very rudimental device inspired by the system Egyptian farmers used to assist chicken eggs to hatch (23, 24). Almost a century passed before a double-walled metal incubator was reported in Russia in 1835 by the physician Johann Georg von Ruehl (25). Despite these two earlier reports, the French physician Jean-Louis-Paul Denucé is considered the author of the first infant incubator with his design devised in 1857. Like the von Ruehl's design, Denucé's incubator was made of a double-walled metal tub heated with water. A few years later,

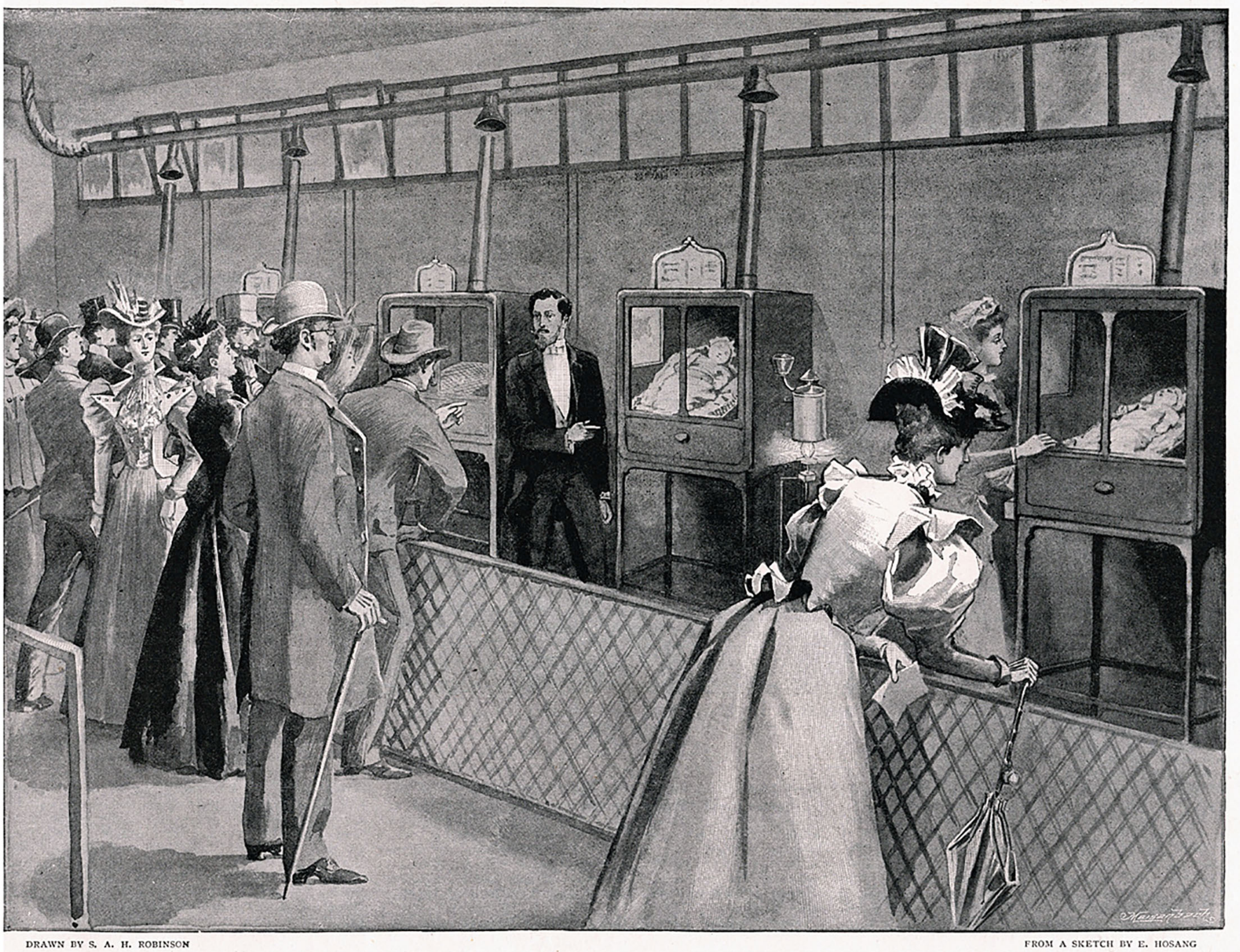

FIGURE 2 | "An Artificial Foster Mother: Baby Incubators at the Berlin Exposition". Display of Lion Incubators in 1896. Retrieved from: The Graphic 1896; 54:461; https://www.epoch-magazine.com/post/mothers-and-machines-on-the-midway-the-curious-case-of-baby-incubators.

in 1860, the German obstetrician Carl Credé and the French obstetrician Stéphane Tarnier developed similar models almost concomitantly. Credé's incubator also consisted of a double-walled metal tub, but it was warmed with water circulating externally to the chamber (26). Tarnier's incubator was more inspired by the Liceti's original design and made from a chicken incubator converted into a newborn care device (**Figure 1**).

With the beginning of 1890, a former French student of Tarnier, Pierre-Constant Budin together with his American pupil Martin Couney marked the beginning of a new era, characterized by the commercial launch of neonatal incubators and their use in exhibitions worldwide (**Figure 2**) (27). The incubator of Budin and Couney was the first to use air heating and even a rudimentary monitor for humidity and temperature. In 1914, Couney settled in Chicago and made the acquaintance of Dr. Julius Hays Hess, who is considered the father of American neonatology. In 1922, Hess designed, conceived, and patented different incubator prototypes (28). His first device consisted in an electrically heated bed with a water jacket and a metal hood for insulation. In 1932, Hess designed and patented a more modern design with a closed chamber equipped with an oxygen dispenser (**Figure 3**) (28, 29).

On a more experimental note, in 1957, the American neonatologist William Silverman started a series of large-scale randomized control trials assessing the causality between thermal care and newborn survival. These studies may well be the first randomized controlled trials in newborn care. Silverman's observations triggered the design of the first closed incubator including surveillance and servocontrol of the temperature (30, 31). High survival rates were independently reported for the Silverman incubator by three different studies performed in the following years (31). However, the subsequent commercialization of the device on a large scale led to the identification of an operational issue in terms of heat loss, such that the

FIGURE 3 | History of Medicine: The Incubator Babies of Coney Island. Retrieved from: https://columbiasurgery.org/news/2015/08/06/history-medicine-incubator-babies-coney-island.

heating system was dismissed and substituted by a convection mechanism (32). These first incubators available for clinical use, were tested by the American neonatologist Paul Perlstein who showed unstable temperatures within servo-controlled incubators (33). By teaming up with the electrical engineer Neil Edwards and the computer programmer Harry Atherton, Perlstein worked on stabilization of incubator temperatures. In 1975, a new device called Alcyon came on the market and was submitted to a 1 year-long trial with over 200 infants (34, 35). Despite its stability in terms of temperature, the Alcyon never reached commercialization because of its complex operation and expensive design. Between 1970 and 1980, with the development of neonatal care practice (i.e., mechanical ventilation), ease of access became fundamental (36). Open incubators were conceived as open-bed devices surrounded by walls more for security reasons and warmed through radiant heat source, hence referred to as radiant warmers. However, because of humidity dispersion, these devices were not adapted for very premature neonates with immature skin and high trans-epithelial water losses (29, 37).

Modern Infant Incubators and Warmers: A Snapshot on the Global Market

Basically, three incubator types are on the market: open (or radiant warmers), closed and transport incubators.

Open incubators are lower priced than closed ones, but more prone to humidity dispersion. Whilst allowing easier access, open incubators do not offer a protective "bubble" around the infant. Moreover, they have high energy consumption requiring a constant and efficient electric energy supply (38).

Closed incubators are designed to provide a stable microclimate, offering an environment where temperature, humidity, and sometimes oxygen can be thoroughly regulated. In addition, the protected space guarantees some isolation from pathogens (through air filters) and noise of the surrounding environment, while still allowing access (38). The concomitant presence of all these operational features in one single device is fundamental considering the overlapping medical conditions newborns may display right after birth (6).

Transport incubators are usually closed, small and minimalistic in their functionality, characterized by intuitive design and interfaces (38).

The incubator market is moderately competitive, as only a handful of major manufacturers, like GE Healthcare and Natus Medical Incorporated (US), Drägerwerk AG & Co. KGaA (Germany), Atom Medical Corporation (Japan), and Phoenix Medical Systems (Pvt) Ltd. (India) account for the most part of its share[4]. The cost of standard incubators varies considerably, spanning form 1,500 U$ (for some transport incubators) to 50,000 U$ (for some closed NICU incubators) (38, 39).

The state-of-the-art devices of GE Healthcare, such as the Giraffe OmniBed Carestation Incubator, the Giraffe and Panda warmer, and the Giraffe shuttle, are high-tech stationary or transport incubators which are characterized by complex design and high price. For these reasons, most "western" incubators are not suitable for LMICs and SSA. Increased complexity often comes with technical faults alongside the need for additional qualified training, which overall further increase their market price (38).

The price range for a simple transport incubator, without taking into account equipment for monitoring or respiratory support, such as the GE Healthcare Lullaby, the INC-TRP from SS Technomed, the TINC-101 from Phoenix Medical Systems, the BT-100 from Zhengzhou Dison Instrument and Meter Co. and the Isolette C2000 from Dräger is on a different scale (from 400 U$ to 10,000 U$) compared to stationary incubators[5]. The Dräger C2000 is one of the 25 best-selling incubators worldwide as it includes thermo-monitoring system and servocontrol (40). The thermo-monitoring allows the concomitant display of a central and peripheral temperature potentially allowing detection of cold stress before hypothermia (40).

The Issue of Hypothermia in SSA

The Adherence to the WHO Warm Chain Procedures for Prevention

The WHO warm chain recommendations are available since almost 25 years, but neonatal hypothermia persists and still kills in SSA (1–4). Hence, these guidelines are either insufficient, inappropriate, or not followed. Some elements of the warm chain may indeed not be applicable in SSA settings. This is for instance partly the case for the environmental temperature at delivery, whether in hospitals or households, that can hardly be controlled to meet the recommendations, remaining strongly exposed and dependent on diurnal and seasonal variations (41). Moreover, the prompt drying and wrapping, placing the infant onto the mother's chest for skin-to-skin contact, and the early initiation of breastfeeding lack consistent practice (41). In rural regions of SSA, both healthcare providers and mothers-to-be have little adequate knowledge of neonatal physiology, appropriate handling, and even simple existing thermal care solutions (13, 41).

Hypothermia appears to represent a major challenge particularly for premature and low-birth-weight newborns, whose births are rising worldwide. About 15 million babies are being born prematurely each year and the highest incidence is in SSA and developing countries[6].

In physiologic terms, the skin of preterm/LBW newborns is immature and has little superficial protection and underlying fat insulation, providing only a limited heat barrier; moreover, LBW infants have a higher ratio of body surface to weight, which physically increases heath loss. Finally, LBW and preterm newborns have only low brown adipose tissue (BAT) storage. BAT is built up during the last weeks of gestation as the first line of metabolic non-shivering thermogenesis in the term newborn (42). Altogether, LBW and premature newborns can produce less heat while being more susceptible to lose it, and therefore, are more prone to cold stress and hypothermia (42). Re-warming neonates highly relies on technology-based solutions.

[4]https://www.mordorintelligence.com/industry-reports/incubators-devices-market

[5]https://bimedis.com/search/search-items/neonatology-neonatal-incubators

[6]https://www.who.int/news-room/fact-sheets/detail/preterm-birth

The Operation of Essential Technologies to Treat Hypothermia in SSA

In SSA, hospitals are most often underfunded and devoid of continuous electricity to guarantee medical device operation (43). Their frequent power cuts place SSA countries among the 20 main electricity access-deficit countries. Moreover, access to electricity does not imply reliability neither good quality, and unscheduled interruptions and voltage fluctuations frequently occur (43). Adequate and reliable electric power supply is vital for standard medical devices and incubators since they are made of complex electronic circuits. Thus, by triggering technical malfunctioning, unstable power supply is in part responsible for newborn mortality by underheating or overheating.

As universally conceived in western countries, market-available infant incubators are ill-adapted for SSA and its unstable electricity profile (44, 45). In SSA, almost all medical devices are imported, either brand-new or regenerated. Despite initial compliance with operational requirements, equipment half-lives are very short because of power cuts, poor maintenance, shortage of spare parts, and improper use (44, 45). Accordingly, about 70% of LMICs' medical devices as partially or completely non-functional (45).

Infant Incubators and Radiant Warmers in Place in SSA

In SSA, the technology-based solutions to treat newborn hypothermia must be robust and affordable. Hence, low-cost devices have been developed in the 90s considering the limited availability of resources in SSA and, more in general, in LMICs.

The first low-cost incubator for these settings was developed in Uganda in 1968 by Oscar van Hemel. This closed incubator, named HEBI (HEmel Baby Incubator), was inexpensive, effective, and easy to assemble and repair. Over 1,400 HEBI incubators have been supplied and are still in use in LMICs[7]. However, the obsolete technology together with the dependence on the Dutch market for shipping and repair, gradually led to the termination of the HEBI production. In 2010, the Baltimore Kiwanis Incubator Foundation (BKIF) developed a similar closed incubator for Central and South American countries. BKIF incubators are low-cost and light, displaying a compact and high-tech design which employs long-lived incandescent light bulbs[8]. A low-cost thermal bag, called Embrace, has been conceived around 2010 and distributed to LMICs by Phoenix Medical Systems from 2016[9]. Embrace is proven to be cost-effective, small, portable, and safe. However, its pouch-like design does not include any system to monitor the temperature. Moreover, issues have been reported in terms of access to the baby, cleaning, and charging (46). The Hot Cot incubator, provided by Inditherm Medical CosyTherm™, is an example of a low-cost and simple model standardly employed in Malawian hospitals. Limitations are mainly related to the fact that this device is not equipped with automated servocontrol (47). In 2010, the Car Part incubator was conceived and essentially made of old car parts. This low-cost design relied on components belonging to obsolete vehicles, which in developing contexts turned out to be expensive and not easy to retrieve. At present, the design entered in disuse mostly for this reason, together with others related to the limited access to the baby and its complex assembly[10]. In 2014, James Roberts won the Dyson Award for a low-cost, portable, and inflatable infant incubator named mOm, that works with batteries and is highly portable. It is even equipped with a screen displaying temperature and humidity. The mOm incubator has a robust design and is currently in the process of being CE marked in Europe as Class IIb device[11]. Recently, a low-cost incubator made of a cardboard chamber has been designed at UMBC and is being field-tested (48). This incubator has been conceived to be halfway disposable after use (the cardboard chamber), and halfway reusable (the heating unit). Its design allows it to be easily transportable and straightforward to assemble, although issues related to robustness and cleaning have been reported (48)[12]. A more recent device is the AUI-Techno, an example of locally designed incubator conceived by the Cameroonian engineer Serge Armel Njidjou. It's local conception and design have been developed to cope with tropical weather and electric power outages, using solar energy as back-up power[13].

A Special Focus on Hypothermia's Prevention and Treatment in Kenya

In Kenya, the current population is about 55 million people, with a growth rate increase of 2.26% from 2020 to 2021[14]. Importantly, 75% of the population lives in rural areas, which undoubtfully provide less healthcare services for both quantity and quality. In Kenya, 21 newborn deaths per 1,000 live births have been reported in 2019 (4), way above the SDG3.2 target of ≤12 deaths every 1,000 live births (see text footnote 2). Considering this rate and that about 1,500,000 live births were officially recorded in the country register, at least 31,500 newborns must have died in 2019[15].

About 50% of the Kenyan population lives in condition of poverty, which implies that children are born in poor households with little access to healthcare services and deliveries that occurs most frequently at home (49, 50). Moreover, in rural Kenya, 16 million people out of the 55 million total population lack access to electricity (43).

In a prospective study conducted in 2016, an overall insufficient adherence to the WHO warm chain protocol to prevent hypothermia was significantly associated with newborn mortality (12). This sub-optimal compliance is attributable to a fundamental mismatch between the needs of the population and

[7] https://hebi-incubator.org/
[8] http://bkif.org/incubator-specifications/
[9] https://www.embraceglobal.org/
[10] https://www.financialexpress.com/archive/a-baby-incubator-made-from-car-parts/716637/
[11] https://www.momincubators.com/
[12] https://news.umbc.edu/low-cost-infant-incubator-developed-at-umbc-completes-successful-clinical-trial-in-india/
[13] https://www.afd.fr/en/actualites/made-cameroon-specially-designed-incubators-premature-babies
[14] https://www.macrotrends.net/countries/KEN/kenya/population-growth-rate
[15] https://knoema.com/atlas/Kenya/topics/Demographics/Fertility/Number-of-births

the offer of services by the healthcare across the country, where a general shortage in human and financial resources is highly noted. In fact, a study conducted among Kenyan counties in 2020 highlighted the lack of physicians and nurses[16].

Specifically, these studies showed that the temperature of the delivery rooms was consistently below the WHO recommendations, almost 50% of the mothers were not educated for newborn thermal care, and rooming in, skin-to-skin contact, and early breastfeeding were often ignored, with an adherence percentage of 10% only for all of them individually. Of note, however, 81.7% of newborns were promptly dried and wrapped, thermal resuscitation practices were observed (64%), as well as early bath avoidance (74%) (12).

In a survey performed in 2018 across 31 healthcare facilities within the county of Nairobi, a shortage of essential infant equipment has been clearly revealed, including warming and resuscitation devices to treat hypothermia (49). Furthermore, a subsequent inspection conducted at the Kenyatta National Hospital (KNH) brought to light that even higher-level Kenyan hospitals were *de facto* unable to provide adequate maintenance and repair services for technical medical equipment (51).

Several strategies have been proposed to promote local production and research to provide SSA with essential technologies. As an example, the Maker Movement for "Maternal, Newborn and Child Health" has been launched in 2013 to empower local partnerships at KNH and foster collaboration with the Kenya National Bureau of Standards for technical guidance, international regulatory frameworks, and staff training (51). Of note, the regulatory capacity for medical devices is very limited in SSA, with only South Africa disposing of regulatory frameworks that are internationally recognized (52). Importantly, this lack of available materials and protocols is limiting the local fabrication capacity, precluding SSA's independence from the international markets (52).

TABLE 1 | Essential features for incubators tailored to the SSA contexts, needs, and end-users.

Features	Context	Research output
Affordability	○ Underfunded health care infrastructures	Low-cost
Robustness	○ Inadequate maintenance and repair, ○ Shortage of spare parts	Smart-tech (essential design, low complexity)
Focused on the end-user	○ Inadequate training ○ Staff shortage	Intuitive assembly, handling, and operation
Based on local needs	○ Local medical protocols ○ Newborn admissions	Fit to local protocols and infant admission loads
Energy efficiency	○ Power outages ○ Lack of access to electricity ○ Inadequate quality of electricity	Design to cope with local electricity profiles; renewable energy
Compatible with the local manufacture	○ Local production capacity ○ Component availability ○ Transport efficiency ○ Sustainability	Empowerment of the local production
Easy cleaning	○ Infections ○ Infrastructure gaps (i.e., inadequate sterilization)	Safe and manageable
Resistant to the tropical environment	○ Harsh environment (humidity, temperature, and dust)	Guaranteed operation in the local environment
Certified	○ Lack of local institutions for regulatory framework (52)	CE/FDA approval overseas

DISCUSSION AND CONCLUSIONS

The Framework of Current Knowledge

Neonatal mortality in SSA is a major burden and a tragic reality which can be summarized in the most part as "*too many tiny babies and not enough medical equipment to provide life-saving newborn care*" (45). Here, the combination of knowledge gaps as well as a general distrust for the current hypothermia prevention strategies make technology-based solutions for treatment particularly indispensable. One key example is represented by the skin-to-skin practice of KMC, an essential measure for the WHO warm chain, which is fundamental for both mother-baby interaction and newborn development. Importantly, KMC also contributes to a substantial reduction of neonatal mortality by hypothermia and is highly effective for LWB and premature newborns. Nevertheless, KMC is insufficiently accepted and practiced in SSA, because of several features, such as poverty, cultural beliefs, and the poorly developed neonatal care units.

Despite being the first key intervention to prevent hypothermia, KMC cannot last 24 h and is unfeasible, for instance, when the mother needs to rest; moreover, KMC becomes also impractical in case of unstable newborns that necessitate constant monitoring. For these reasons, technology-based solutions most be in place as a complementary tool to KMC "for" the mother and the infant and not "between" them.

Even though essential, the shortage of robust and affordable incubators to treat hypothermia and their frequent improper operation when available must be considered as a significant contributing factor for neonatal death (together with prematurity, asphyxia, respiratory distress syndrome, and infections).

Access to solid and performing technologies may significantly reduce the burden of neonatal disease and mortality (53). Infant medical devices are in fact core components of healthcare development and represent unavoidable building blocks for sustainable health progress. The demand for low-cost and high-tech infant medical equipment remains high, as many healthcare facilities call for efficient and adapted equipment to deliver the quality and quantity of healthcare services needed.

Local ministries of health need to invest more in the perinatal sector, improve the quality of maternal, antenatal,

[16]Mohiddin A and Temmerman M, "COVID-19 Exposes Weaknesses in Kenya's Healthcare System and What Can Be Done" (The Conversation) <http://theconversation.com/covid-19-exposes-weaknesses-in-kenyas-healthcaresystem-and-what-can-be-done-143356> accessed 9 September 2021.

and postnatal care. By strengthening neonatal medicine and neonatal care in fact, they will also promote engagement and empowerment of mothers and mothers-to-be, couples, families, and communities.

All in all, there is an urgent need for holistic, yet affordable, technology-based interventions to sensitize health workers, produce knowledge, promote awareness, and ultimately save lives in countries which desperately need so. For SSA countries to be able to adopt a large-scale local production of medical devices, regulatory institutions and frameworks should be established to parallel the local fabrication capacity, ultimately allowing SSA's independence from the overseas market.

Evidence reinterpretation: call for research focused on technology-based solutions tailored to the SSA context, the need, and the end-user.

It is of paramount importance that medical devices for LMICs are specifically designed to cope with their harsh settings. Inputs form the local context, need, and end user are needed to design equipment that will enable the provision of skilled care to newborns. Given the unstable power profiles and the critical aspects related to large-scale production and maintenance, it is highly necessary to research for robust, energy efficient, low-cost, tropicalized, user-friendly solutions adapted to local protocols (**Table 1**). In addition, smart-tech equipment and incubators will allow standardized collection of data on thermal care, which is indispensable for the generation of clinical and epidemiological evidence as well as for raising medical awareness. Such data can allow the gathering of evidence-based information for policy-makers and boost prevention- and treatment-focused interventions in the next future.

SUMMARY

- Neonatal mortality in SSA is a major burden.
- The lack of robust and affordable incubators to treat hypothermia must be considered as determinant of neonatal death.
- Gaps in the knowledge and distrust around the measures to prevent hypothermia make technology-based solutions for treatment indispensable.
- Technology-based solutions must be in place as a tool "for" and not "between" the mother and the infant.
- Medical devices in SSA are imported and not specifically designed to cope with its harsh settings.
- Inputs form the local contexts, and end-users are necessary, to design equipment that will enable the provision of skilled care to newborns.
- Access to solid and performing technology-based solutions may significantly reduce the burden of neonatal disease and mortality in SSA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

GBP, CG, SS, MAR, SM, KS, MR-K, MK, and REP contributed to the conception and design of the work, alongside with the acquisition, analysis, and the data interpretation, drafting and editing of the work content, the final approval of the revised version for publication, and ensured accuracy and integrity. All authors contributed to the article and approved the submitted version.

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Magnitude and Determinants of Postnatal Mothers' Knowledge of Essential Newborn Care at Home in Rural Ethiopia

Tamirat Getachew, Merga Dheresa, Addis Eyeberu, Bikila Balis and Tesfaye Assebe Yadeta*

School of Nursing and Midwifery, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

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Andrew Steenhoff,
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United States

***Correspondence:**
Tamirat Getachew
tamirget@gmail.com
orcid.org/0000-0002-0057-9062

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Introduction: Globally, nearly three million children die in the neonatal period. Although there is scant information about rural mothers, the enhancement of mothers' knowledge and skills toward essential newborn care (ENC) is a vital aspect in the reduction of newborn illness and mortality. Thus, this study aimed to assess the magnitude and determinants of mothers' knowledge of ENC.

Methods: A community-based cross-sectional study was conducted among recently delivered women using a multistage sampling method in Chole woreda. Data were collected *via* face-to-face interviews. A multivariate logistic regression model was used to identify the determinant factors with the level of knowledge. Odds ratios with a 95% confidence interval was used to describe association and significance was determined at a P-value < 0.05.

Results: Data from 510 mothers were employed for analysis. Overall, 33.5% (95% CI: 29.4, 37.6) of the mothers had good knowledge of ENC. Antenatal care (ANC) visits [AOR: 2.42; 95% CI: (1.50, 3.88)], counseled about ENC during ANC [AOR: 5.71; 95% CI: (2.44, 13.39)], delivery at health institutions [AOR: 2.41; 95% CI: (1.30, 4.46)], religion [AOR 1.99, 95% CI: (1.25, 3.16)], and educational level [AOR = 1.64 95% CI: (1.10, 2.51)] were significantly associated with knowledge of ENC. About 74, 75, and 41% of mothers practiced appropriate cord care, breastfeeding, and thermal care, respectively.

Conclusion: Three out of 10 mothers had a good level of knowledge of ENC. Knowledge gaps identified pertained to cord care, breastfeeding, and thermal care. There is opportunity to enhance maternal knowledge of ENC through improving access to ANC and institutional delivery.

Keywords: essential newborn care, knowledge, postnatal mothers, newborn, home delivery

INTRODUCTION

Children are most commonly vulnerable to disease, injury, and death during the neonatal period (1). Globally, nearly three million children lose their life before celebrating 1 month of life. Almost 99% of neonatal mortality occurs in low-income nations, including Ethiopia, where health care systems are weak and most of the mothers deliver at home, attended by untrained birth attendants (2, 3). Applying appropriate health interventions that are accessible, reasonable, and tolerable to mothers may prevent most of these neonatal deaths in low-income countries (4).

The World Health Organization (WHO) declared essential newborn care (ENC) as a comprehensive approach to advance the health of newborns and mothers through interventions throughout the perinatal period (during pregnancy, childbirth, and postnatal period) (1, 5). ENC comprises instant drying and covering of newborns following birth, starting skin-to-skin contact, hygienic cord care, eye care, immunization, sooner initiation of breastfeeding, and late washing. Despite the importance of ENC, its enactment was not satisfactory, especially among those delivered at home in Ethiopia (6, 7).

Globally, most neonatal deaths can be averted through standing maternal and child health curriculum which are associated to clean cord care for the prevention of sepsis, regulating temperature, and early initiation of breastfeeding (2, 8). In addition to skill enhancement and equipping health professionals, enhancing the knowledge of mothers regarding ENC is very critical to increasing the quality of ENC. Knowledge gaps and durable cultural principles influence newborn survival at the moment the neonate is at home with the mother. Therefore, the enhancement of mothers' knowledge and skills toward ENC are vital aspects to sustain life, growth, and development of neonates and reducing neonatal morbidity and mortality (9).

Evidence from research carried out in Mekelle, Ethiopia indicates that only one-third of mothers were knowledgeable regarding ENC. Good knowledge (mothers who responded correctly to at least 75% of questions) of ENC showed association with mothers who were educated, counseled during childbirth and postnatally, were knowledgeable of newborn care, and had good knowledge of newborn signs of illness (10).

However, neonatal death is still high, and the Ethiopian government has implemented various health interventions including health care provider training, improving referral systems, integrating health services, applying packages of the Health Extension Program, and regular vaccination (11). However, most women still give birth at home with untrained birth assistants, which may promote the exercise of harmful traditional practices (12). Little emphasis was given to newborn care until the placenta is delivered. This came with delays in drying or covering and delayed skin-to-skin contact with frequent positioning slightly away from the mother's side. Inappropriate knowledge of mothers and caregivers during this period could decrease the quality of newborn care, which may threaten newborn well-being, possibly increasing neonatal mortality (13).

Although a mother's knowledge of ENC is highly effective in the reduction of neonatal mortality and has been broadly encouraged, information on women's knowledge and its determinant factors toward ENC in a study setting is inadequate. Moreover, most studies have focused on health professionals' knowledge of ENC and on scanty evidence about postnatal women's knowledge of ENC in Ethiopia, particularly in rural settings, where home delivery is high. Thus, this article aimed to assess the magnitude and determinants of mothers' knowledge of ENC in rural Ethiopia.

METHODS AND MATERIALS

Study Period and Setting

This survey was studied at Chole woreda from March 1 to 30 in 2019. The administrative center for Chole woreda is Chole town. There are 4 health centers, 18 health posts, 10 private clinics, and eight pharmacy shops in the woreda. Each health center serves a population of 15,000–25,000 and health posts are attached to each health center (each health post serves 3,000–5,000 people in the woreda). Maternal and child health care services, including antenatal care (ANC), postnatal care (PNC), family planning, and immunization services, were available in the facilities free-of-fee-services. A total of 20 kebeles represented the woreda. The annual report in 2017 of the Chole health office indicated that the health coverage of the woreda attained 57.3% (14).

Study Design and Population

This is a cross-sectional study conducted at the community level among postnatal mothers who delivered within 6 months before the study period. Postnatal mothers who delivered in the past 6 months at Chole woreda but were incapable to communicate because of serious illness or impaired cognition at the time of the data collection were not included in the study.

Sample Size Determination and Sampling Procedure

The sample size was computed using a single population proportion formula by assuming a confidence level of 95% = 1.96, a margin of error (d) = 5%, design effect = 1.5, and prevalence of postnatal mothers' knowledge of ENC ($P = 31\%$) in accordance to a study conducted in southern Ethiopia in 2017 (15). It also included a 5% non-response rate. Finally, 520 postnatal mothers were included. A multi-stage cluster sampling method was used to select postnatal mothers. Chole woreda has 20 kebeles (the smallest administrative unit; 16 rural and four urban), five and two kebeles from the rural and urban areas, respectively, were included through a simple random sampling technique. The final sample size was allocated to each kebele proportional to the number of their population. Finally, study participants were randomly recruited from the sampling frame found from records of health extension workers of the kebele. All eligible study participants were interviewed until the desired sample size was achieved.

Abbreviations: ANC, antenatal care; CSA, central statistics agency; ENC, essential newborn care; HEWs, health extension workers; PNC, postnatal care; SDGs, sustainable development goals; WHO, World Health Organization.

Data Collection Methods

The data were collected using an interviewer-administered structured questionnaire adapted from previous studies (10, 16–18). The questionnaire included socio-demographic, obstetrics, and reproductive characteristics, knowledge about essential newborn care, and exposure to counseling during the postnatal period. Seven trained health professionals collected the data under the supervision of three health professionals. A face-to-face interview was conducted among volunteer mothers through structured and pretested questionnaires.

Measurement and Operational Definitions

Some of the questions on several features of newborn care included practice regarding immunization, thermal care, breastfeeding, cleanliness, and umbilical cord care.

Knowledge level was assessed based on questions on various aspects of essential newborn care (e.g., knowledge about immunization, thermal care, breastfeeding, and umbilical cord care were assessed). The values were coded as 1 = Correct response and 0 = Incorrect response. Finally, based on the median score, a composite variable from these questions was generated to categorize mothers as having "Good/poor knowledge."

Good Knowledge

Those postnatal mothers who were able to answer the knowledge questions above or equal to the median (17).

Poor Knowledge

Those postnatal mothers who were able to answer the knowledge questions below the median (17).

Essential newborn care refers to the postnatal mothers' care for newborns, which includes early breastfeeding, cord care, eye care, immunization, neonatal danger signs, and thermal care (19).

Safe cord care refers to the maintenance of the umbilical cord. Particularly, ensuring that the cord clean and dry without application of any substance on the cord stump except for medically indicated medications, such as chlorhexidine (10).

Optimum thermal care includes wrapping the newborn in a clean and dry cloth and the delay in bathing for 24 h to avoid hypothermia (10).

Early breastfeeding is the act of immediately starting breastfeeding within the first hour of birth without pre-lacteals and feeding the child with colostrum (10).

Data Quality Control

A pretest among 10% of the computed sample size was carried out to test the quality of the questionnaires. Each question under the questionnaire was checked for completeness and consistency. The questionnaire was translated into Amharic and Afan Oromo languages (language spoken by the local community). The data collectors and supervisors were trained. The collected data was double data entered into Epi Data version 3.1 software.

Data Processing and Analysis

Descriptive analysis by statistical package for social sciences (SPSS) version 20 stat calc was presented with a proportion of 95% CI. Continued variables were described using a median and interquartile range. The results were shown using frequencies, percentages, tables, and figures. A chi-square assumption was checked before fitting the model. The Hosmer-Lemeshow statistic and Omnibus tests were checked to assure the model's goodness of fit. A binary logistic regression model was utilized to detect the association between determinants and the outcome variable. All variables with $P \leq 0.25$ in the bivariate analysis were exported to multivariate analysis to control all possible confounders. The degree of a statistical association between determinants and outcome variables was assessed by using an odds ratio at a 95% level of confidence. Statistical significance was stated at a P-value < 0.05.

Ethical Considerations

The Ethical clearance was granted by the College of Health and Medical Sciences, Institutional Health Research Ethics Review Committee (HU-IHRERC) of Haramaya University. Additionally, an official letter that allows us to conduct this study was obtained from the woreda health bureau and governmental officials. After explaining the purpose of the study and their right,

TABLE 1 | Socio-demographic characteristics of mothers who delivered in the past 6 months in Chole woreda, Ethiopia in 2019 ($n = 510$).

Variables	Categories	Frequency	Percent
Residence	Urban	177	34.7
	Rural	333	65.3
Age of mother	15–24	105	20.6
	25–34	340	66.7
	35–44	65	12.7
Educational level	Primary and below	178	34.9
	Secondary and above	332	65.1
Marital status	Single	9	1.8
	Married	467	91.6
	Divorce/separated	27	5.3
	Widowed	7	1.4
Husbands educational level	Primary and below	273	58.5
	Secondary and above	194	41.5
Religion	Orthodox	372	72.7
	Muslim	113	22.4
	Protestant	25	4.9
Ethnicity	Oromo	253	49.6
	Amhara	255	50.0
	Tigre	2	0.4
Sex of child	Male	269	52.7
	Female	241	47.3
Occupation	Governmental employee	22	4.3
	Private employee	28	5.5
	Housewife	353	69.2
	Merchant	29	5.7
	Farmer	67	13.1
	Other*	11	2.2

*Other-student and daily laborer.

informed and voluntary signed consent was obtained from each study participant.

RESULTS

Basic Characteristics of Mothers

From the total ($n = 520$) sample size, 510 mothers were employed for the analysis, yielding a 98.1% of response rate. The median (IQR) age of the mothers and their neonates was 28.48 (4.68) years and 2.7 (1.5) months, respectively. The majority of the mothers were married 467 (91.6%) and were rural residents 333 (65.3%; **Table 1**).

Obstetrics Services and Reproductive Health Characteristics

Of the total respondents, about 363 (71.2%) of the mothers were multiparous and 63 (87.6%) of respondents had at least one prior miscarriage. Among mothers who had ANC (483), 237 (49.1%) of them had four or more visits to hospitals or clinics and the majority (392; 76.9%) were visited by Midwives/Nurse followed by health extension workers (HEWs; 84, 16.4%). Regarding the place of delivery, 134 (26.3%) of the mothers gave birth at home. Vaginal delivery accounted for 487 (95.5%) of births, while instrumental delivery and caesarian section accounted for 12 (2.9%) and 8 (1.6%), respectively (**Table 2**).

The Relationship Between the Number of ANC Visits and Home Delivery

Of 483 (94.7%) participants who had ANC visits, 375 (77.6%) mothers delivered at health institutions, and 108 (22.4%) delivered at home. The study revealed that having an ANC visit was protective to attending the subsequent home delivery (**Figure 1**). Almost 99% of mothers who had no ANC visits delivered at home.

Exposure to Counseling During Antenatal Care (ANC) Visit

Among the total mothers (483; 94.7%) who had at least one ANC follow-up, only 364 (75.4%) respondents got counseling during their ANC visits. The most commonly attended counseling during ANC visits were counseling about family planning 170 (46.7%), maternal nutrition 143 (39.3%), and breastfeeding 136 (37.4%). On the other hand, counseling on danger signs of pregnancy, immunization, ENC, and neonatal danger signs were poorly addressed areas in all counseling during ANC, in which only 106 (29.1%), 98 (26.9%), 90 (24.7%), and 21 (5.8%) of mothers were counseled respectively.

Exposure to Counseling During the Postnatal (PNC) Period

None of the respondents had completed all three WHO-recommended PNC visits. However, 381 (74.7%) of respondents had their first or immediate PNC visits, and only 138 (36.2%) of respondents received PNC counseling. During the postnatal visit, the least received counseling was ENC (13.6%) and neonatal danger signs (5%) counseling, respectively (**Table 3**).

TABLE 2 | Obstetrics and reproductive health characteristics respondents in 2020 ($n = 510$).

Variable	Categories	frequency	Percent
Para	1	112	22.0
	2–4	363	71.2
	≥5	35	6.9
Abortion history	Yes	63	12.4
	No	447	87.6
ANC	Yes	483	94.7
	No	27	5.3
No. of ANC visit	3 or fewer visits	246	50.9
	4 or more visits	237	49.1
ANC seen by	Physician	7	6.7
	Midwifery/Nurses	392	76.9
	HEWs	84	16.4
Got ANC counseling	Yes	364	75.4
	No	119	24.6
Delivery place	Health institution	376	73.7
	Home	134	26.3
Assisted by	Health professional	376	73.7
	TBA	54	10.6
	TTBA	68	13.3
	Relative (friend)	12	2.4
Immediate PNC	Yes	381	74.7
	No	129	25.3
Care-giver during PNC	Midwife/nurse	325	85.3
	HEWs	47	12.3
	Other*	9	2.4

*Other- physician and health officer.
TBA, traditional birth attendant; TTBA, trained traditional birth attendant.

Knowledge About Essential Newborn Care (ENC)

Most of the respondents (88.3%) knew at least one component of ENC. However, about 33.5% (95% CI: 29.4, 37.6) of the study participants had good knowledge of ENC and responded above the median score (≥4), while 339 (66.5%) had poor knowledge about ENC and responded below the median score (<4). About 75% of respondents think that the newborn baby should not be nursed in a room separated from his/her mother after delivery.

Cord Care

The majority (377; 73.9%) of the respondents practiced safe cord care. Different instruments were used to tie a cord, of which 250 (49%) stated they used a sterile cord tie, 80 (15.7%) stated unsterile materials were used, and 48 (9.8%) of them did not know the material used. Regarding materials applied on the cord, 298 (58.4%), 34 (6.7%), and 178 (34.9%) stated that they applied nothing, anti-septic solution, and butter, respectively. From the total respondents, 388 (76.1%) have reported that they would go to a health facility if a sign of cord infection was seen. On the other hand, 102 (20%) of women would give home remedies,

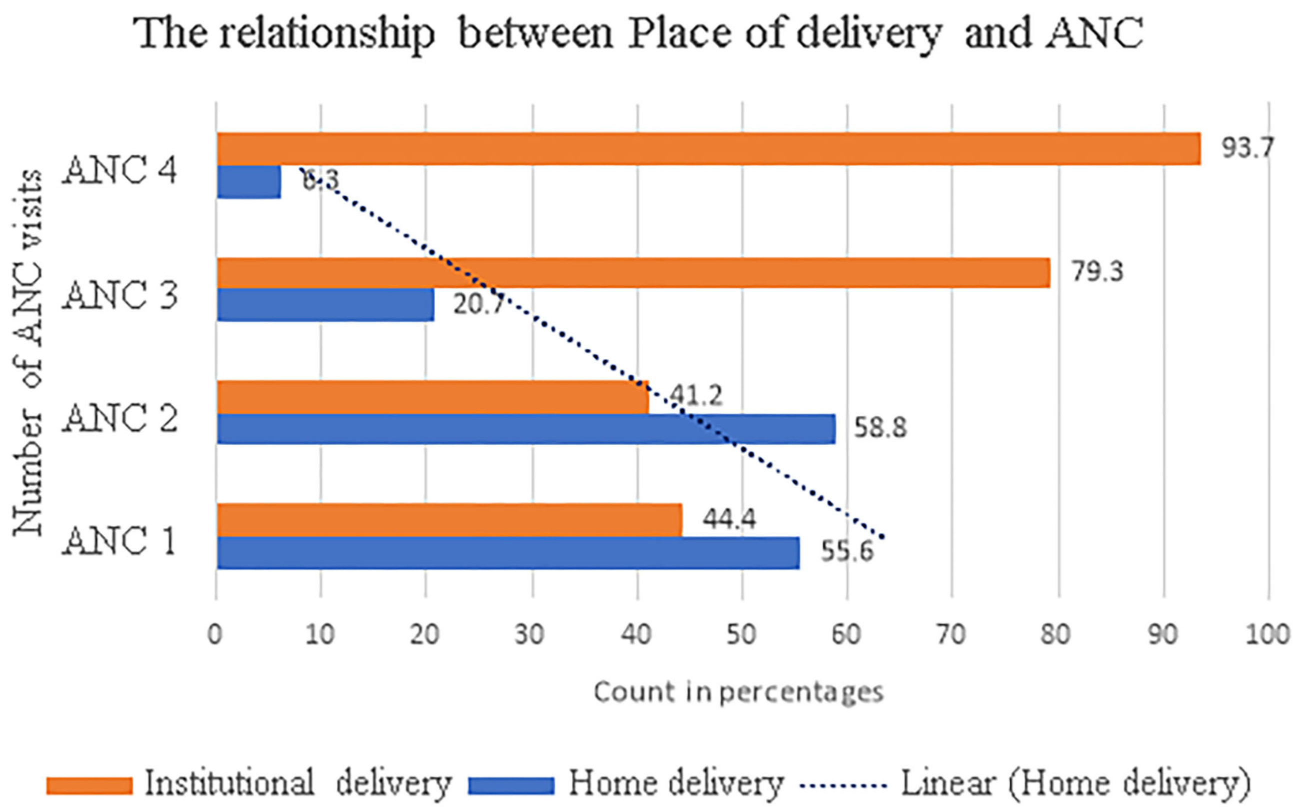

FIGURE 1 | The association between place of delivery and antenatal care (ANC) visit.

TABLE 3 | The type of counseling received by respondents during the postnatal care (PNC) visit at Chole woreda, Ethiopia in 2019 ($n = 138$).

Type of counseling received during PNC visit	frequency	Percentage (%)
Immunizations	102	73.9
Family planning	97	70.3
Childbirth complications	43	31.2
Nutritional advice	67	48.6
Breastfeeding	114	82.6
Essential newborn care	19	13.6
Neonatal danger signs	7	5
Postnatal care	40	29.1

while 20 (3.9%) of them stated that they would delay until it heals by itself.

Breastfeeding

When participants were asked about breastfeeding, 386 (75.7%) specified that breastfeeding initiation time was within 1 h after delivery, and 124 (24.3%) of them stated breastfeeding should be initiated after 1 h. Only 203 (39.8%) mothers feed colostrum to their newborn, while the rest do not fed the newborn colostrum due to lack of awareness. Additionally, 350 (68.6%) stated that they exclusively feed their newborns until the first 6 months, while 301 (59%) reported that newborns should exclusively breastfeed until 6 months.

Thermal Care and Immunization

Of the total respondents, 209 (41%) initiated bathing within 24 h and 301 (59%) initiated bathing after 24 h of delivery. Approximately 422 (82.7%) mothers used a cape to cover the head of the newborn, and approximately 122 (23.9%) study participants exercised skin-to-skin contact with the mother immediately after delivery. From 203 (39.8%) mothers who knew that the newborn needed to be vaccinated at birth, only 27 (5.3%) of respondents immunized their newborn immediately after delivery.

Determinants of Mothers' Knowledge of Essential Newborn Care

To detect independent determinant factors of ENC, nine variables from socio-demographic, reproductive, and obstetric characteristics and informational related factors having a P-value of ≤ 0.25 on bivariate analysis were fitted into the final model. The multivariable logistic regression analysis revealed that good ENC knowledge level among mothers is significantly associated with the number of ANC visits, place of delivery, mother's religion, and educational status.

TABLE 4 | Bivariate and multivariate logistic regression for determinants of mothers' knowledge of essential newborn care in Chole woreda, Ethiopia in 2019 (*n* = 510).

Variables	Level of knowledge of ENC		Odds ratios	
	Poor frequency (%)	**Good frequency (%)**	**COR (95% CI)**	**AOR (95% CI)**
Residence				
Rural	242 (72.7)	91 (27.3)	1	1
Urban	97 (54.8)	80 (45.2)	2.19 (1.50, 3.21) **	1.37 (0.88, 2.16)
Maternal education level				
Secondary and above Primary and below	152 (67.9)	72 (32.1)	1.12 (0.77, 1.62)	1.64 (1.07, 2.51) *
	187 (65.4)	99 (34.6)	1	1
Partner's education level				
Secondary and above Primary and below	29 (85.9)	5 (14.1)	3.11 (1.18, 8.17) *	4.85 (0.67, 35.07)
	310 (65.1)	166 (34.9)	1	1
Religion				
Christian	283 (71.3)	114 (28.7)	1	1
Muslim	56 (49.6)	57 (50.4)	2.53 (1.65, 3.88) **	1.99 (1.25, 3.16) *
Number of ANC				
1–3	191 (77.6)	55 (22.4)	1	1
4 and above	121 (51.1)	116 (48.9)	3.33 (2.25, 4.93) **	2.42 (1.50, 3.88) **
Counseled during ANC				
No	90 (75.6)	29 (24.4)	1	1
Yes	222 (61.0)	142 (39)	1.99 (1.24, 3.17) *	5.71 (2.44, 13.39) **
Marital status				
Currently unmarried	34 (79.1)	9 (20.9)	1	1
Currently married	305 (65.3)	162 (34.7)	2.01 (0.94, 4.29)	2.85 (0.52, 15.61)
Place of delivery				
Home	117 (87.3)	17 (12.7)	1	1
Health institution	222 (59.0)	154 (41.0)	4.77 (2.76, 8.26) **	2.41 (1.30, 4.46) *
PNC visit				
No	290 (70.6)	121 (29.4)	1	1
Yes	49 (49.5)	50 (50.5)	2.45 (1.56, 3.83) **	1.28 (0.77, 2.14)

*Significant with $P < 0.05$ and ** Significant with $P < 0.001$.
PNC, postnatal care; CI, confidence interval; COR, crude odds ratio; AOR, adjusted odds ratio; ANC, antenatal care.

Antenatal care visit completion was found to be one of the significant determinant factors of a mother's good knowledge of ENC. Mothers who had four or more ANC visits were 2.42 times more likely to have good knowledge of ENC compared to mothers who had less than four ANC visits [AOR: 2.42; 95% CI: (1.50, 3.88)]. The odds of good knowledge were higher among mothers who get counseled about ENC during ANC [AOR: 5.71; 95% CI: (2.44, 13.39)]. The odds of knowing about ENC was 2.41 among mothers who gave birth at health institutions [AOR: 2.41; 95% CI: (1.30, 4.46)] compared to mothers who gave birth at home.

Mothers who are Christian were almost two times more likely to have good knowledge of ENC compared to those whose religion was Muslim [AOR 1.99, 95% CI: (1.25, 3.16)]. Mothers who attained secondary and above educational levels were 1.64 times [AOR= 1.64 95%CI: (1.10, 2.51)] more probable to have good knowledge of ENC compared to mothers who attain primary and lower education levels (**Table 4**). On the other hand, the age of the mother, parity, partner educational status, source of information, and history of abortion were not significantly associated with maternal knowledge of ENC.

DISCUSSION

The first few minutes and hours immediately after birth are the most critical period in the life of a newborn. Hence, preventing neonatal morbidity and mortality requires equipping mothers with accurate knowledge of newborn care to ensure proper practices. In this study, only 33.5% of mothers had good knowledge of ENC. This may result in failure to achieve the national goal of reducing neonatal mortality from 28 to 11/1,000 by 2020 (20). This result has a prodigious inference on the survival of the neonates, opposing preventable disease, and future development and productivity.

The magnitude of good knowledge of ENC in this study is in line with prior studies from Ethiopia (10, 21) despite being lower than studies conducted in Nekemte city, Ethiopia (19, 22) and Ghana (23). This could be due to the study setting variation since this study was conducted in a rural area, a place where access to health facilities and health professionals is deprived and where traditional home practice is widely exercised. Additionally, poor quality postnatal services, counseling, and inadequate home visits could aggravate this issue. Mothers with poor knowledge of ENC are more likely to use harmful traditional practices which may affect the health and growth of newborns and create a negative impact on the current global and national plan to reduce neonatal mortality by 2030 (24).

The finding on the level of good knowledge in this study is also higher than the studies conducted in India (25) and Bangladesh (26). This might be due to the study population in India consisting only of primiparous mothers, while adolescent women (aged 15–19 years) who had ever been married with noninstitutional births were the study population for the study conducted in Bangladesh. Therefore, adolescents, primiparous mothers, and mothers who delivered at home might be less knowledgeable about ENC. Moreover, differences in the socio-cultural composition of the study groups and differences in the study period might be the reason for this discrepancy.

The care of the umbilical cord always needs special attention as it can function as the entry point for infections. Almost 26.1% of the respondents in this study practiced unsafe cord care and 34.9 % of them applied butter to the cord immediately after delivery. This is supported by findings from Ethiopia (19, 27). Locally, many people believe that applying butter, animal dung, or Vaseline would lubricate the cord and prevent dryness and cord and neonatal cloth attachment (21). However, this could result to be a source of infection which later complicates the survival of the neonate. In summary, this indicates that mothers had a lack of knowledge about appropriate cord care.

Regarding breastfeeding knowledge, 75.7% of mothers stated that breastfeeding should be initiated within 1 h. Although exclusive breastfeeding should be the only source of nutrition and energy for infants up to 6 months of age, only 59% of them reported that newborns should exclusively be breastfed until 6 months. On the other hand, WHO universally recommends that colostrum, the first milk that flows within the first few days after delivery, is the perfect food for every newborn, but only 39.8% of mothers feed colostrum to their newborn in this study. This is in line with a study conducted in southern Ethiopia (21), though incongruent to others (19, 22). This incongruity could be due to service delivery of information and demonstration about effective breastfeeding techniques for breastfeeding mothers or variation in health service utilization, culture, and taboos about breastfeeding (colostrum) within various areas. Early initiation of breastfeeding is encouraged as it stimulates breast milk production and facilitates the release of oxytocin, which helps in uterine contraction and reduces postpartum hemorrhage (28). Culturally, mothers milk out the first milk from the breast before attaching the newborn to the breast because they believe that the initial breast milk/colostrum is dirty and not nutritious. Therefore, they believe that the newborn must be supplemented with pre-lacteal feeds like butter and honey (29).

Hypothermia has significant contributions to neonatal morbidity and mortality in Ethiopia (30). According to this study, the thermal care practiced among respondents included initiating newborn bathing within 24 h after delivery (41%), using a cape to cover the head of the newborn (82.7%), and the exercise of skin-to-skin contact with the mother immediately after delivery (23.9%). Although the proportion varies, similar studies were being reported (10, 19). Strong cultural beliefs could be the main reason for common thermal care malpractices. The baby is seen as dirty after delivery, particularly if the vernix was visible, leading to the stigmatization of the mother. This is due to the belief that the vernix is the result of sperm secondary to late trimester sexual practice (31).

The presence of the routine provision of ANC had a significant impact on the mother's level of knowledge about ENC, which is consistent with studies done in Mekelle, Ethiopia (10), Kenya (32), and Ghana (23). Maternal and child health care are interrelated. The more women who adhere to the continuum of maternal and childcare, the more women who will know the benefits of care, understand health appointments, and improve their communication with care providers. Therefore, we recommend that the maternal and child health services, including ANC and PNC, should be further strengthened, especially at rural community levels.

Educated mothers were more likely to be knowledgeable about ENC. The role of maternal education as an important determinant factor of a mother's knowledge of ENC has also been reported by other studies (10, 22). Education leads to an increased level of awareness regarding maternal and neonatal illnesses, health-seeking behavior, and availability of services, which may sensitize the family to decide and utilize health care provided at various health care facilities (7). The Ethiopian government assigned HEWs in each kebeles to improve maternal and child health service delivery in the district by delivering appropriate information about the different available services to the mothers at the community and household level. But this alone does not seem to be enough to increase the level of maternal knowledge. The findings from this study also revealed that there is a significant association between mothers' religion and knowledge of ENC. A similar finding was reported in Uganda (33). This implies there is a need to further study with analytical study design for future researchers.

Institutional delivery is also significantly associated with ENC. Mothers who delivered at health institutions were about four times more likely to have good knowledge of ENC when compared to mothers who delivered at home. The result was in line with a previous study reported from Ghana (23). This might be because mothers who deliver at the health facility may get better counseling regarding ENC, PNC, and danger signs. Hence, they feel quite confident about their health and the health of their newborn. This indicates that home deliveries may be missed opportunities to promote ENC's benefits for mothers and newborns. In addition, the findings suggest that there is a need to improve the quality of maternal health care services (counseling or health education and promotion) at the rural community level.

Strength and Limitation

Since this study was carried out at the community level in rural Ethiopia, it has the chance to gather the opinion of participants at the grass-roots level and helps to produce means to improve the services and knowledge gaps of ENC among the rural community. However, as a limitation, the study was focused on reported rather than observed knowledge levels of ENC. In addition, due to the cross-sectional nature of the study, it could be difficult to see the causal relationship between the independent and the outcome variable. Again, the study assumes homogeneity among the kebeles which may not be true in real circumstances.

CONCLUSIONS

Based on this study, mothers' knowledge level of ENC was significantly low in the study area. Antenatal care visits, counseling during ANC place of delivery, delivery place, religion, and maternal educational status were factors significantly associated with the mother's knowledge of ENC. Cultural practices, such as tying the cord with unsterile materials, applying butter on the newborn cord, giving home remedies for cord infection, avoiding colostrum feeding, and home delivery practices, were common. Therefore, it is better to give special attention to ensuring that education should focus on women for antenatal care follow-up, encouraging institutional delivery, and inspiring counseling to rural and illiterate mothers.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Haramaya University, College of Health and Medical Sciences, Institutional Health Research Ethics Review Committee (IHRERC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TG: conceptualization, investigation, methodology, project administration, analysis, writing—original draft, and writing—review and editing. MD: conceptualization, methodology, writing—review, writing—review and editing, and supervision. AE: conceptualization, methodology, writing—original draft, and writing—review and editing. BB: investigation, methodology, writing—original draft, and writing—review and editing. TY: conceptualization, analysis, writing—review and editing, and supervision. The co-authors wrote the manuscript. All authors were involved in reading and approving the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.860094/full#supplementary-material

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Human and Economic Cost of Disease Burden Due to Congenital Hypothyroidism in India: Too Little, but Not Too Late

*Ramesh Vidavalur**

Department of Neonatology, Cayuga Medical Center, Ithaca, NY, United States

Background: Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation. Implementing newborn screening (NBS) in >52 countries enabled early detection and to initiate treatment of neonates with CH. India is yet to implement a national NBS program even though an estimated 5–15% of sick newborns suffer from genetic and metabolic disorders. Recent pilot studies confirm that the CH incidence rates range from 1 in 500 to 1 in 3,400 live births. Our objective was to estimate overall incidence rates of congenital hypothyroidism and to evaluate the costs and benefits of implementing universal NBS for CH in India.

Methods: We used the best available epidemiological and cost data to synthesize incidence rates and screening costs for CH in India. We conducted a meta-analysis of country-specific published literature and included 14 studies to calculate baseline CH incidence rates. We used two models to estimate intellectual disability in unscreened cohorts. Disability-adjusted life years (DALY) were calculated to quantify burden of disease utilizing disability weights. Direct costs including screening, confirmatory tests, and treatment costs were obtained from public and private market sources. Economic benefits were calculated from lost DALY using human capital approach and value of statistical life methods, utilizing gross national income (GNI) per capita data and value of statistical life year (VSLY), respectively. Cost discounting was used to estimate the present value of future benefits over lifetime of affected newborns.

Results: The incidence rate of CH in India is 72 (95% CI: 58, 85) cases per 100,000 live births. Based on this data, 1 in 1,388 (95% CI: 1166, 1714) infants were diagnosed with CH in India for the year 2018. The estimated annual incidence ranged from 14,000 to 20,730 cases, and those at risk for intellectual disability ranged from 5,397 to 13,929 cases. Estimated discounted and undiscounted lost DALYs were 57,640 and 410,000, respectively. Direct annual costs for universal screening for CH in India is around USD187 million. Based on current incidence and expected severity of sequelae, economic losses ranged from USD 159 million to 1.1 billion. Benefit–cost ratios ranged from 1.8 to 6.

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Ashish K. C.,
Uppsala University, Sweden

Reviewed by:
Kanshi Minamitani,
Teikyo University Chiba Medical Center, Japan
Kiran More,
Sidra Medicine, Qatar
Dipesalema Joel,
University of Botswana, Botswana

***Correspondence:**
Ramesh Vidavalur
rav2016@med.cornell.edu

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Conclusions: Universal NBS for CH is one of the healthcare interventions that is beneficial to prevent morbidity and cost saving. The cumulative economic benefits, derived from prevention of intellectual disability, assuming cost effectiveness threshold of three times of gross domestic product per capita, far outweigh the direct and indirect costs of screening, treatment, and surveillance throughout the life of the affected individuals. Our analysis strongly supports the argument for investing in NBS that provides good value for money and would yield substantial financial gains for the country.

Keywords: congenital hypothyroidism, newborn screening, economic evaluation, value of statistical life, disability adjusted life year, newborn, India, Benefit-Cost Analysis

INTRODUCTION

Congenital hypothyroidism (CH) is the most common preventable cause of intellectual disability worldwide (1, 2). Primary congenital hypothyroidism is the result of developmental defects of the thyroid glands, mainly due to thyroid agenesis or dysgenesis or dyshormonogenesis that can lead to severe acute and chronic clinical symptoms including long-term intellectual impairment. Neonatal screening for CH, first implemented almost half a century ago, offers a window of opportunity for timely diagnosis of CH, to initiate appropriate treatment and prevent long-term morbidity. It is estimated that 7 in 10 newborns with CH are born in areas that have no neonatal screening programs (3).

Most of the industrialized nations have implemented healthcare system changes to incorporate newborn screening in the last five decades to detect early, treat promptly, and eliminate neurodevelopmental impairment from CH (4). Unfortunately, majority of nations with the highest burden of CH does not have effective, established universal newborn screening programs to eliminate disease burden. This poses considerable public health challenge to limit preventable chronic morbidity in population (3), as it is one of the most common causes of cognitive impairment in newborns that has an enormous societal impact if screening is not done and replacement therapies are not initiated in timely manner (5). Early detection and prompt treatment of CH (within the first 2 weeks of life) are essential to optimize the neurocognitive outcome, linear growth, the onset and progression of puberty, pubertal growth, and final height of affected neonates (6).

Moreover, morbidity from noncommunicable diseases is increasingly recognized to have sizeable economic impact on households, industries, and societies, both via the consumption of health services and via losses in income, productivity and human capital (**Figure 1**). Fortunately, in the past two decades, early initiation of treatment and improvement in the overall management of CH patients have resulted in better cognitive and motor developmental outcomes, comparable with those of controls (7).

Historically, all the newborn screening programs in high-income countries are implemented as a part of public health mandated programs with centralized facilities for testing, reporting, and surveillance. From welfare economics' point of view, one of the main reasons for countries to do this is the belief that early detection of a few disorders can offer societal health benefits by mitigating or reducing healthcare burden on worse outcomes of these disorders. Selecting these disorders for national newborn screening panels is based on several factors—cost of screening, feasibility, and extent of health benefits.

With >25 million annual births and prevalence of CH varying between 1 in 600 to 1 in 1,700 newborns (8–11), India screens <2% of newborns for CH annually (12, 13). Currently, only 5 out of 26 states have started, or are in the process of, establishing universal screening programs to screen for CH. In addition, the World Health Organization recommends introduction of genetic services in countries with infant mortality rates of <40 per 1,000 live births. As India is striving to achieve Sustainable Development Goals (SDG), especially to keep neonatal mortality rate under 12 per 1,000 live births with the introduction of the India Newborn Action Plan within the framework of Janani Suraksha Yojna and other national health mission programs, time is ripe to introduce programs to reduce disease burden of noncommunicable diseases and other nonfatal risks in newborns (14).

To make public healthcare decisions at the policy level, it is essential to have a detailed analysis on cost savings, cost effectiveness, or cost benefit of necessary public programs. Many of these analyses are based on multiple assumptions. It not only requires frequency of health conditions along with various outcomes in the context of with or without interventions but also need to take economic and opportunity costs into consideration. Thus, quantifying the health and economic benefits of population-level screening program, especially in newborns, is challenging. While India's MDG and SDG commitments to reduce infant mortality have been substantially successful, there is an urgent need for renewed focus on morbidity-preventing strategies, such as universal newborn screening for common conditions that poses considerable long-term health risks. Countrywide screening programs, if implemented efficiently in a populous country like India, can provide safety nets, minimize adverse outcomes in relatively

Abbreviations: CI, confidence interval; CH, congenital hypothyroidism deficiency; DALY, disability-adjusted life year; GNI, gross national income per capita; VSL, value per statistical life; VSLY, value per statistical life year; YLL, years of life lost; YLD, years lived with disability.

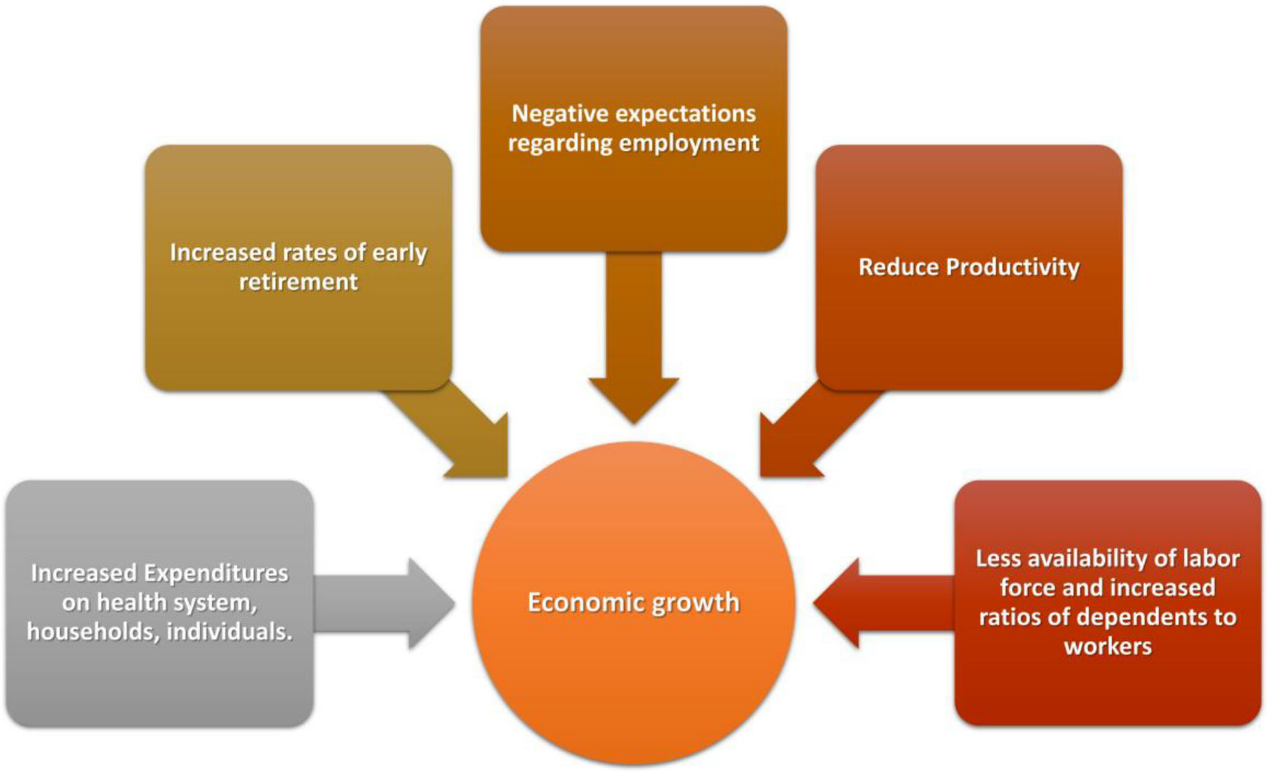

FIGURE 1 | Effects of poor health on economy.

modest number of disease-afflicted cases, encompassing overall improvement in societal health. At the same time, these programs should also be thoroughly evaluated beforehand to estimate projected net health benefits in order to invest in strong health systems that prioritize newborns with appropriate healthcare resource allocation.

The purpose of this study was to estimate the burden of disease, assess economic losses from reduced human capital secondary to disease-associated morbidity, and to examine benefits and costs from universal newborn screening program for CH in India. These data will inform country-specific estimates of CH in India and allow prioritization of resource allocations toward child health.

METHODS

Design and Population

Estimates of congenital hypothyroidism in India: Literature searches of electronic databases including PubMed, OVID, and Google Scholar were performed using a combination of search terms: (((((Congenital hypothyroidism) AND (India))) AND (prevalence)) OR (incidence)) AND (newborn screening)). Of 13,330 studies identified by our initial search, we selected 178 publications that were relevant to our study. Among them, we identified 14 studies that provided incidence data. We excluded studies that had <500 subjects to minimize heterogeneity and to maximize precision and accuracy. We performed a random effects meta-analysis using standard techniques to calculate pooled estimates with 95% confidence intervals. We assessed heterogeneity using I^2 and publication bias with Eggers test. Statistical significance was set at $p < 0.05$. For population parameters, including population, births, life expectancy, and GNI, relevant sources are shown in **Table 1**.

Years of Life Lost, Years Lost Due to Disability, Disability-Adjusted Life Years

The disability-adjusted life years (DALY) is defined as the sum of years of life lost (YLL) and years lost due to disability (YLD) (i.e., DALY = YLL + YLD) (18, 19). YLL was not calculated in this study as mortality is uncommon in cases with CH.

To perform a patient-focused analysis including the lifetime impact of congenital hypothyroidism on DALY, the morbidities in terms of intellectual disability anticipated with degree of severity of hypothyroidism were included in the calculation of YLD. Specifically, YLD was calculated by multiplying the incidence (I) of intellectual disability due to untreated congenital hypothyroidism by a disability weight (DW) (17) associated with the degree of disability and the anticipated duration of that state with intellectual disability (L) (i.e., YLD = I × DW × L). The DW was included in the calculation of the YLD

TABLE 1 | Input parameter pooled estimate for incidence of hypothyroidism in India.

Input parameters		Lower	Upper	References
Number of Births	24,164,360			MOHFW, GOI
Incidence of CH	0.000720	0.000583	0.000857	Point estimate from our study
Frequency of Sequelae-Model 1				Barden et al. (15)
Mild ID	0.4			
Moderate ID	0.25			
Severe ID	0.15			
Frequency of Sequelae-Model 2				ACMG, Committee on Genetics (16)
Mild ID	0.27			
Moderate ID	0.021			
Severe ID	0.019			
Disability weights				Mathers et al. (17)
Mild ID	0.29			
Moderate ID	0.43			
Severe ID	0.82			
GNI per capita	$6,427			World Bank (PPP method)
Costs				
Screening Costs	$173,500,105			Our estimates
Confirmation Assay cost	$125,020	$101,196	$148,843	
Medication Costs:	$8,501,347	$6,881,341	$10,121,354	
Follow up Costs				
Physician visits	$4,000,634	$3,238,278	$4,762,990	
Laboratory costs	$1,500,238	$1,214,354	$1,786,121	

ID-Intellectual Disability; Costs converted from INR to 2018 USD.

account for severity of disease and disability. They range from 0 (perfect health) to 1 (worst possible health state). Frequencies of mild, moderate, and severe intellectual disability (ID) from CH and associated disability weights were obtained from existing literature (15, 16), as the accurate prevalence and projection of long-term outcomes of overt disabilities (intellectual or physical or behavioral) at population level, in the absence of established CH screening program, is difficult to capture and prone to have substantial variations as most of existing prevalence and outcome estimates come from published clinical case series literature. To quantify the magnitude of outcomes in the absence of screening, we developed two models—Model 1 and Model 2. Model 1 is based on the frequency of intellectual disability due to CH from previous economic evaluations from the United States and Australia (15, 47) where they followed evidence from clinical case series in the prescreening era. Model 2 is based on the American College of Medical Genetics (ACMG) committee estimates of intellectual impairments, used in cost utility analysis of newborn screening programs in the United States (19, 48). We used country-specific life expectancy assuming constant disability from undiagnosed and untreated CH for the lifetime of the neonate. In summary, one DALY is equivalent to loss of 1 year of healthy life.

The notation "DALYs (r,K,ß)" is used to describe the results: where r = discount rate, K = age-weighting modulation factor, and ß = parameter from the age-weighting function. DALYs estimates were presented with [DALYs (0.03, 1., 0.04)] and without [DALYs (0,0,0.04)] age weighting and discounting (18).

Costs

We included screening, confirmation, treatment costs from industry sources, academicians, and the Government of India website (http://www.nppaindia.nic.in/). Cost data are presented in the Supplementary Information. Costs for screening tests were obtained from two resources—Medplus Labs and Genes n' Life labs, two private sector labs. These costs were cross checked with nationally funded pilot project costs and also correlated well with inflation-adjusted costs for screening in the United States and recent region-specific literature (20, 21). Screening costs included supplies for sample collection, consumables, logistics, assay, labor, overhead costs, and confirmation assay. Clinical care costs included annual physician visits, annual laboratory testing, and medications. Frequency of testing and physician visits were modeled as per clinical practice guidelines recommended by the Indian Society of Pediatric and Adolescent Endocrinology for newborn screening for primary CH (22, 23).

Economic Value of Lost Disability-Adjusted Life Years

Human Capital Approach

Using the human capita (HC) approach, we estimated lost productivity from three values—number of disabilities, number of DALY losses, and gross national income per capita (GNI) (24). GNI per capita is an estimate of average individual productivity to the national economic output in a given year. Monetizing the number of DALYs lost from a specific cause can be used as proxy for non-productive years from an individual perspective that reflects the lost opportunity of significant domestic productivity of a developing country. DALY losses with 95% uncertainty levels were used in the calculations, and sensitivity analysis was done with different discount rates (3%, 5%, 7%) and assumed reductions in morbidity to estimate the present value of future benefits. We modeled these estimates as follows:

Based on the total number of disabilities, YLD lost was calculated using a life expectancy of 67 years. We used GNI per capita (PPP—*purchasing power parity* method) to estimate the total economic value of estimated disabilities. Economic losses were calculated from monetizing lost DALYs and multiplying these life years with GNI per capita. Based on clinical evidence, we assumed that there would be no mortality from CH (YLL), and total YLD reflect total DALY (**Table 3**).

$$\text{Economic productivity loss} = \text{DALY lost} \times \text{GNI per capita} \times \text{discount factor}$$

Value of Statistical Life Approach

The value of monetized DALY is based on the value of statistical life year (VSLY), derived from VSL as described elsewhere (25). VSL reflects individual willingness to pay (WTP) for a reduction in mortality and morbidity, and we followed recent reference case benefit cost analysis guidelines to calculate the value of morbidity reductions (26). We used this method to determine ranges of three VSL estimates in a standardized sensitivity analysis as follows:

Step 1. First estimate calculated by multiplying GNI per capita by a factor 160;

Step 2. Multiplying GNI per capita by a factor of 100;

Step 3. Extrapolate VSL from a US estimate to India using an elasticity of 1.5 using the formula: $VSL^{India} = VSL^{USA} \times (GNI^{India}/GNI^{USA})^{1.5}$

Then, we obtained VSLY, which mirrors and individual's WTP. A constant VSLY was derived from a standard, population-averaged, country-specific VSL estimate by dividing life expectancy at the average adult population age, which is equivalent to one half of life expectancy at birth as a rough proxy. This constant VSLY is considered as an indirect estimate of monetized lifetime value of a DALY. Finally, we measured the lifetime economic productivity gains by multiplying VSLY with the number of lost DALYs and sensitivity analysis done for estimated reductions in morbidity (**Table 4**). All costs and benefits are presented in United States Dollars (USD).

RESULTS

Prevalence of Congenital Hypothyroidism and Its Sequelae

Our random effects meta-analyses (**Table 2**) show the pooled estimate of incidence of congenital hypothyroidism in newborns at 1 in 1,387 (95% CI: 1 in 1,165, 1 in 1,714). This estimate translated to 72 (95% CI: 58, 85) cases per 100,000 live births. There was marked heterogeneity in incidence of CH in different geographical regions among the included studies ($I^2 = 56\%$). We determined that, out of 26 million births in the year 2018, 17,412 (95% CI: 14,094, 20,730) infants were expected to be diagnosed with CH. Among those diagnosed with CH, if untreated, the number of infants at risk for intellectual disability from Model 1 and Model 2 were 13,929 newborns (range: 11,275–16,584) and 5,397 (range 4,369–6426), respectively (**Table 3**).

TABLE 2 | Pooled estimate for incidence of hypothyroidism in India.

References (8, 10, 27–33)	Incidence		
	1 in	95% CI	
Desai et al. (27)	2,481	1,322	20,095
Desai et al. (28)	2,804	1,696	8,093
Rama Devi and Naushad, (29)	1,700	1,064	4,223
Sanghvi and Dewakar, (10)	500	275	2,749
Kishore et al., (30)	1,042	719	1,893
Sudha et al., (31)	900	673	1,357
Kaur et al. (32)	1,400	959	2,594
ICMR Chennai (34)	727	531	1,155
ICMR Delhi (34)	1,141	793	2,032
ICMR Hyderabad (34)	1,383	918	2,800
ICMR Kolkata (34)	1,255	842	2,460
ICMR Mumbai (34)	1,544	1,000	3,382
Verma et al. (8)	1,706	1,429	2,117
Verma et al. (33)	1,486	899	4,288
Point Estimate with 95% CI ($I^2 = 56\%$)	1,388	1,166	1,714

TABLE 3 | Severity of congenital hypothyroidism (CH) morbidity.

Severity of CH	Expected No of Infants with Sequelae (Range)	
	Model 1	Model 2
Mild ID	6,964 (5,637–8,292)	4,701 (3,805–5,597)
Moderate ID	4,354 (3,523–5,182)	365 (295–435)
Severe ID	2,611 (2,114–3,109)	330 (267–393)
Total	**13,929 (11,275–16,584)**	**5,397 (4,369–6,426)**

ID, Intellectual Disability.

Estimated Disability-Adjusted Life Years Loss

Considering the average estimate of affected CH cases with neurological sequelae, the net DALYs lost in Model 1, with and without discounting or age weighting were 194,076 and 410,267 respectively. Model 2 estimates ranged from 57, 640 and 121, 849 with and without discounting, respectively (**Table 4**).

TABLE 4 | Lost disability adjusted life years (DALYs) from CH related intellectual disability.

		Mild ID	Moderate ID	Severe ID	Total
Model 1	Lost DALY (0,0,0.4)*	137,348 (111, 175-163, 520)	127,283 (103, 028-151, 538)	145,636 (117,884-173,388)	410, 267 (332,087-488,446)
	Lost DALY (0.03,1,0.04)*	64,972 (52,591-77, 353)	60,211 (48,739-71, 685)	68,893 (55,765-82,021)	194,076 (157,093-231,059)
Model 2	Lost DALY (0,0,0.4)*	92,710 (75,043-110,376)	10,692 (8,654-12,729)	18,447 (14,932-21,962)	121,849 (98,629-145,067)
	Lost DALY (0.03,1,0.04)*	43,856 (35,499-52,213)	5,058 (4,094-6,022)	8,726 (7,064-10,389)	57,640 (46,657-68,624)

**Disability-adjusted life year representation DALY (r,K,b) is used to describe the results where r, discount rate; K, age weighting modulation factor; b, parameter from age-weighting function; Ranges were given in brackets; ID, Intellectual disability; CH, Congenital hypothyroidism.*

TABLE 5 | Estimated lost economic productivity—human capital method.

			Lost Productivity in USD (Range)		
		DALYs (Range)	**3%**	**5%**	**7%**
Model 1	DALYs (0,0,0.4)	410,267 (332,087–488,446)	$1,133,817,984 (917,758,954–1,349,874,250)	$788,300,083 (597,610,482–878,987,884)	$553,725,062 (448,207,861–659,240,913)
	Benefit-Cost Ratio		6 (4.8–7.1)	3.9 (3.1–4.6)	2.9 (2.3–3.5)
	DALYs (0.03,1,0.04)	194,076 (157,093–231,059)	$536,350,374 (434,143,786–638,556,963)	$349,251,407 (282,698,279–415,804,534)	$261,938,555 (212,023,709–311,853,401)
	Benefit-Cost Ratio		2.8 (2.3–3.4)	1.8 (1.5–2.2)	1.4 (1.1–1.6)
Model 2	DALYs (0,0,0.4)	121,849 (98,629–145,067)	$336,743,114 (272,572,090–400,908,611)	$219,274,586 (177,488,803–261,056,770)	$164,455,939 (133,116,602–195,792,577)
	Benefit-Cost Ratio		1.8 (1.4–2.1)	1.1 (0.94–1.4)	0.87 (0.7–1)
	DALYs (0.03,1,0.04)	57,640 (46,657–68,624)	$159,294,480 (128,941,751–189,649,972)	$103,726,638 (83,962,070–123,493,005)	$77,794,978 (62,971,553–92,619,754)
	Benefit-Cost Ratio		0.86 (0.68–1)	0.56 (0.44–0.65)	0.42 (0.33–0.49)

Cost Per Case Detected

At incidences of 1:1,165, 1:1,387, and 1:1,714, the cost to detect each primary CH case is $9,050, $10,775, and $13,312, respectively. For countrywide CH screening and subsequent management, it costs approximately $187 million (range $184–$190 million) annually.

Economic Benefits

Using the HC approach, Model 1 and Model 2 estimates of the economic benefits of reducing undiscounted DALYs lost due to CH were $1.1 billion (range: $917 million to $1.3 billion) and $336 million ($272 million to $400 million), respectively. With discounting, they ranged from $434 to $638 million and $128 to 189 million (**Table 5**). Using standardized sensitivity analysis, values of VSL ranged from $347,634 to $1.02 million, and values of VSLY estimates ranged from USD $5,189 to $15,348 (**Table 6**).

Estimated net monetary benefits were $348 million (range $249–448 million) and $819 million (range 639–1 billion) from HC and VSL methods, respectively. Using the same econometric methods, benefit–cost ratios from HC methods ranged from 2.8 (95% CI: 2.3, 3.4) to 6 (95% CI: 4.8,7.1) when evaluated with discounted benefits and costs at 3% over a lifetime. Benefit–cost ratios were much higher ranging from 10.7 to 31.7 when VSL methodology was used to monetize lost DALYs. Overall, our analysis revealed newborn screening costs $457 (range: $389–$556) per DALY averted.

DISCUSSION

This study confirms pooled prevalence rate of CH at 7 per 10,000 live births, comparable with other subnational studies and worldwide prevalence rates. Our population model predicts the present value of future benefits, if uniform national screening, implemented at an expense of $187 million, outweighs the costs incurred. We estimate that the costs incurred to avert loss of a DALY remain at $457–$966, which is less than the one-time GDP per capita and cost effective as per WHO—CHOICE guidelines (35).

Now in the sixth decade, universal newborn screening for different disorders reduced significant disease burden in terms of morbidity and mortality worldwide. In the last decade, after extensive preparatory and execution phases to test the feasibility and collect data after newborn screening across five regions covering >100,000 newborns, a large collaborative study (34) from the Indian Council of Medical Research has recommended universal newborn screening for CH with an estimated overall

TABLE 6 | Estimated lost economic productivity—value of statistical life method.

			Model 1			Model 2		
			Estimated Loss of Productivity* **in USD (Range)**		**Benefit-Cost Ratio**	**Estimated Loss of Productivity*** **in USD (Range)**		**Benefit-Cost Ratio**
	VSL[a]	**VSLY**[b]			**Range**			**Range**
			DALYs (0.0.0.4)	**DALYs (0.3, 1, 0.04)**		**DALYs (0.0.0.4)**	**DALYs (0.3, 1, 0.04)**	
VSL_{160}	1,028,320	30,696	$12,593,604,819 (10,193,782,204–14,993,396,738)	$5,957,380,069 (4,822,145,485–7,092,614,653)	31.7–67.1	$3,740,291,453 (3,027,527,561–4,452,993,953)	$1,769,324,322 (1,432,188,843–2,106,490,498)	9.4–19.9
VSL_{100}	642,700	19,185	$7,871,003,012 (6,371,113,878–9,370,872,961)	$3,723,362,543 (3,013,840,928–4,432,884,158)	19.8–41.9	$2,337,682,158 (1,892,204,725–2,783,121,221)	$1,105,827,701 (895,118,027–1,316,556,561)	5.8–12.4
VSL $USA^{c}_{1.5}$	347,634	10,377	$4,257,397,850 (3,446,113,092–5,068,672,232)	$2,013,953,706 (1,630,175,960–2,397,731,453)	10.7–22.6	$1,264,444,059 (1,023,486,882–1,505,380,481)	$598,138,315 (484,166,193–712,120,814)	3.1–6.7

[a] *Value of statistical life (VSL): Country level population average value of VSL estimate using GNI per capita and assumed income elasticity-based on GNI- India: $6,427(2018); GNI-USA: $57,900 (2017).*
[b] *Value of statistical life year (VSLY): A constant VSLY averages health status over lifetime.*
[c] *This VSL is extrapolated from US estimate to India using an income elasticity of 1.5. This option is preferred as it takes the efforts taken to reduce mortality and morbidity risk in low and middle income countries.*
* *Productivity calculated from monetized DALYs using VSLY over life time.*

prevalence of 1 in 1,130 newborns. The same study concluded that there were significant differences in prevalence of CH among different regions and early identification followed by subsequent timely thyroid replacement therapy resulting in better developmental quotients and growth velocity.

To further support timing and initiation of therapy and the critical role of thyroid hormone on normal brain development and function, few other clinical case series (36, 37) showed that burden of disease depends on time of diagnosis and treatment even after achieving euthyroid status once the diagnosis has been made. They have shown that infants who had delayed diagnosis and treatment had lower intelligent quotient (IQ) scores, scholastic performance, and behavioral problems. In contrast, a study from South Korea concluded that IQ scores, measured by the Weschler Intelligence Scale, were within normal limits when treatment started within 2–8 weeks of diagnosis of CH. Several regional retrospective studies from India have confirmed, in the absence of universal newborn screening, the average age of diagnosis is between 3 and 5 years, and the main reasons are lack of awareness among parents, community, and even among primary care physicians, which can lead to permanent sequelae of CH (38–40). Even if treatment for CH is started before 3 months of age, but later than 1 month, to prevent loss of IQ, many of these infants show some degree of impairment in school performance, speech, and fine motor skills later (41). A recent Irish longitudinal study (42) showed that rates of hypothyroidism in infants that were treated were 1 per 1,000 live births. If we apply that rate to 26 million births in India, we can expect around 26,000 infants that would need treatment, which is within the range of our modeling estimates.

Another recent Government-sponsored national household survey of persons with disabilities in India noted that the number of persons with onset of disability were 86 per 100,000 population, and applying this rate to a population of 1.35 billion, India suffers from significantly lower labor force participation rates, lower worker population ratio, and higher costs of disability support (43). As CH impairs optimal human development, economic losses from decreased labor productivity could be even larger than estimated. It is estimated that each one-point drop in IQ is estimated to reduce lifetime earnings by 1% (44). One study from Sweden found that even in cases of subclinical CH, testing showed an average IQ decrease by 7 points (45). Furthermore, a case series published from a tertiary referral center at the dawn of newborn screening confirmed that 65% of CH patients had an IQ of <85 and another 19% showed profound intellectual disability (46). Multiple large epidemiological follow-up studies concluded that earlier identification and treatment results in better neurodevelopmental outcomes.

Considering the history of newborn screening, a recent review (3) noted that only 29.3% of global births were screened for CH, and majority of the nonscreened infants are born in countries lacking nationwide newborn screening programs. The same study estimates that, across Asia, around 29,480 CH cases miss an opportunity of early screening and related benefits. If we consider these regional estimates, India accounts for >50% of affected newborns.

Poor health among children has remained too high for too long, despite decades of declaring agreements to reduce the burden by committing investments in maternal and newborn health. The newborn screening program promises to help in reducing health inequality, improve productivity, increase family savings, and strengthen the national economy. Saving one DALY through newborn screening costs less than $1,000, which is much smaller than VSLY and costs a fraction of gross domestic product per capita in India. Our analysis shows, even with minimal estimated benefits by discounting, that if we can reduce estimated DALY loss by 40%, implementing newborn screening for CH is cost effective.

Strengths of the Study

To our knowledge, this is the first study to estimate and quantify the burden of congenital hypothyroidism in India. Given the resource restraints, we sought to understand the returns better in terms of health gains if we find resources to implement newborn screening and empirical benefit in preventing a proportion of disabilities caused by CH. For this, we followed three steps. First, we tried to quantify the burden of CH in terms of DALYs for births in year 2018. Over the last 2 decades, DALYs have been used as a key metric in estimating disease burden and monitoring public health. Second, we calculated the relative costs of implementing a comprehensive screening program, and finally, we analyzed the monetary value of avoided disability as the discounted present value of future earnings over their lifetime using various economic methods.

Limitations of the Study

As with all cost-effectiveness studies for any healthcare interventions, our results are limited by available evidence regarding prevalence, frequency of morbidity, screening costs, and quality of life. Another challenge to estimate accurate benefits of NBS is lack of data regarding willingness to pay for health gains, country-specific utility or disability weights, accurate frequency of adverse health outcomes in the absence of screening, and absence of reliable population-based data on late diagnosis and treatment rates. We tried to minimize bias as much as possible by incorporating existing evidence, established estimates, and conducted sensitivity analysis. Costs for radio isotope imaging were not included as there is lack of universal availability and affordability, especially in rural areas. Indirect costs, such as lost parental income and disability care costs, were also not included due to paucity of data and lack of published evidence. General challenges include lack of public awareness and evidence of uptake rates even if universal newborn screening for CH is offered countrywide. Specific challenges include building core infrastructure, enhancing public laboratory and data systems, close surveillance, and follow-up systems to optimize outcomes.

CONCLUSIONS

CH is one of the leading causes of intellectual disability in India. Newborn screening for CH in India seems to be one of the precious healthcare intervention programs that could be beneficial to every newborn, parent, community, and society-at-large. The impact of early identification and follow-up management in preventing lifelong morbidities for CH is undisputable. Our analysis strongly supports the argument of investing in NBS programs that provide good value for money and would yield substantial financial gains for the country. In addition to being cost effective and cost saving in the long term, broader implementation of screening programs might lay a strong foundation for better, healthy future for next generation, and maintain stronger productive workforce for sustainable development of better India. As a few states started implementing newborn screening for CH, it is time to focus on adopting universal newborn screening public health policy and needed resources. Coordinated efforts between healthcare professionals, policymakers, parents, and other stakeholders, including public–private partnerships, may help in building a lasting and successful newborn screening program in India.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RV conceptualized the study, collected the data, carried out the initial analysis, drafted the initial manuscript, reviewed and revised final manuscript, and agreed to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.788589/full#supplementary-material

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Enteral Feeding Practices for Very Preterm and Very Low Birth Weight Infants in Nigeria and Kenya

Olukemi O. Tongo[1], Macrine A. Olwala[2], Alison W. Talbert[3], Helen M. Nabwera[4,5], Abimbola E. Akindolire[1], Walter Otieno[2,6], Grace M. Nalwa[2,6], Pauline E. A. Andang'o[6], Martha K. Mwangome[3], Isa Abdulkadir[7], Chinyere V. Ezeaka[8], Beatrice N. Ezenwa[8], Iretiola B. Fajolu[8], Zainab O. Imam[9], Dominic D. Umoru[10], Ismaela Abubakar[4], Nicholas D. Embleton[11,12] and Stephen J. Allen[4] on behalf of the Neonatal Nutrition Network (NeoNuNet)†*

[1] College of Medicine, University of Ibadan/University College Hospital, Ibadan, Nigeria, [2] Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu, Kenya, [3] KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya, [4] Liverpool School of Tropical Medicine, Liverpool, United Kingdom, [5] Alder Hey Children's Hospital NHS Trust, Liverpool, United Kingdom, [6] Department of Nutrition and Health, Maseno University, Maseno, Kenya, [7] Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, [8] College of Medicine, University of Lagos/Lagos University Teaching Hospital, Lagos, Nigeria, [9] Lagos State University Teaching Hospital, Lagos, Nigeria, [10] Maitama District Hospital, Abuja, Nigeria, [11] Newcastle University, Newcastle upon Tyne, United Kingdom, [12] The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

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Grace Muhoozi, Kyambogo University, Uganda

***Correspondence:**
Alison W. Talbert
atalbert@kemri-wellcome.org

† The complete membership of the author group can be found in the Acknowledgments

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Background: Optimizing nutrition in very preterm (28–32 weeks gestation) and very low birth weight (VLBW; 1,000 g to <1,500 g) infants has potential to improve their survival, growth, and long-term health outcomes.

Aim: To assess feeding practices in Nigeria and Kenya for very preterm and VLBW newborn infants.

Methods: This was a cross-sectional study where convenience sampling was used. A standard questionnaire was sent to doctors working in neonatal units in Nigeria and Kenya.

Results: Of 50 respondents, 37 (74.0%) were from Nigeria and 13 (26.0%) from Kenya. All initiated enteral feeds with breastmilk, with 24 (48.0%) initiating within 24 h. Only 28 (56.0%) used written feeding guidelines. Starting volumes ranged between 10 and 80 ml/kg/day. Median volume advancement of feeds was 20 ml/kg/day (IQR 10–20) with infants reaching full feeds in 8 days (IQR 6–12). 26 (52.0%) of the units fed the infants 2 hourly. Breastmilk fortification was practiced in 7 (14.0%) units, while folate, iron, calcium, and phosphorus were prescribed in 42 (84.0%), 36 (72.0%), 22 (44.0%), 5 (10.0%) of these units, respectively. No unit had access to donor breastmilk, and only 18 (36.0%) had storage facilities for expressed breastmilk. Twelve (24.0%) used wet nurses whilst 30 (60.0%) used formula feeds.

Conclusion: Feeding practices for very preterm and VLBW infants vary widely within Nigeria and Kenya, likely because of lack of locally generated evidence. High quality research that informs the feeding of these infants in the context of limited human resources, technology, and consumables, is urgently needed.

Keywords: feeding practices, very preterm, very low birth weight, Nigeria, Kenya

INTRODUCTION

Globally, about 20.5 million newborn infants were born with birthweights <2,500 g in 2015, 90% of whom were from low- and middle-income countries (LMICs) (1, 2). Nearly half of under 5 deaths are among neonates (infants < 28 days old) (3). Eighty percent of neonatal deaths occur in low birthweight (LBW) infants, which includes both preterm infants born before 37 completed weeks gestational age and infants who are small for gestational age (SGA) i.e., weight <10th percentile for gestational age. Preterm birth is the single most important cause of death in the neonatal period accounting for up to a million neonatal deaths annually (2, 4, 5). Amongst LBW infants, very low birth weight (VLBW; 1,000 g to <1,500 g), and very preterm (born 28 to <32 weeks gestational age) are even more at risk, with higher incidences of late onset sepsis (LOS), necrotising enterocolitis (NEC), feeding intolerance and ultimately, mortality (6, 7).

Optimizing early nutrition in very preterm and VLBW neonates has the potential to improve their survival, growth, neurodevelopment, and long-term health outcomes. Early feeding strategies for preterm infants vary widely across the world and, although optimal postnatal growth rates have not been established, there is a general consensus to aim for a gestation-equivalent fetal growth rate (8). Noteworthy is that preterm infants have higher nutritional requirements than term infants. To achieve this, an energy intake of 110 to 135 Kcal/kg/day and protein intake of 3.5 to 4 g/kg/day in VLBW infants is recommended (9). Failure to meet recommended nutrient intakes results in poor growth and is associated with increased short-term risks such as LOS and predisposes them to long-term neurodevelopmental impairment and adult onset metabolic and cardiovascular disease (8, 10–12).

The majority of available evidence on feeding strategies in hospitalized very preterm/VLBW infants is derived from high income countries (HICs) with limited data from sub-Saharan Africa (sSA) (13). The implementation of recommended strategies is fraught with challenges in the context of resource limitations, a common problem in sSA. Early initiation of enteral feeds and exclusive feeding with breastmilk and fortification of human milk for hospitalized very preterm/VLBW babies is common in high income countries due to the availability of breastmilk banks and fortifiers, which are not available in most centers in sSA (14). In addition, early parenteral nutrition used in HICs, to provide the necessary nutrients whilst full enteral feeds are established, is not widely available and affordable in most of sSA.

In 2011, in recognition of these challenges in LMICs, the World Health Organization (WHO) emphasized early and exclusive breastmilk for preterm babies with formula supplementation only in infants with sub-optimal growth trajectories (15), by which stage key periods for brain growth and differentiation may have been missed. Evidence-based feeding guidelines require high quality research and are essential in resource constrained settings. To achieve this, it is essential to collect data on existing feeding practices.

We conducted a survey to describe feeding practices in hospitalized very preterm/VLBW infants among neonatal care practitioners in Nigeria and Kenya as part of the Neonatal Nutrition Network project (https://www.lstmed.ac.uk/nnu), to identify the diverse challenges and mitigating factors in the context of limited resources. These data will inform the prioritization and design of guidelines and interventions to optimize nutrition in these vulnerable infants in sSA.

METHODOLOGY

Study Design and Setting

This was a cross-sectional survey conducted between February 1, 2018, and April 30, 2019 among pediatricians and neonatologists working in neonatal units in Nigeria and Kenya. Convenience sampling was used.

Study Population and Sampling

A standard questionnaire was sent to doctors working in neonatal units in public and private hospitals in Nigeria and Kenya through the mailing lists of the Nigerian Society of Neonatal Medicine (NISONM) (16) and the Kenya Paediatric Association (KPA) (17). Additional participants (neonatologists) were approached during a workshop on neonatal nutrition in Ibadan, Nigeria, in March 2018. The questionnaires were anonymized although respondents had the option to provide their names. Names of the hospitals and the level of care provided were requested as well as the designation of the respondents. In Nigeria, where there were multiple responses from individual participating centers, that of the most senior doctor was selected. In Kenya, individual clinicians were approached from each hospital.

Data Collection

The questionnaire was emailed to Nigerian Society of Neonatal Medicine (NISONM) members and returned by e mail. Online forms prepared using REDCap software were emailed to members of the Kenya Paediatric Association (KPA). The questions included the number and level of personnel working in the doctor's neonatal unit and the available equipment and laboratory services. Information on the number of patients, reasons for admission and the feeding practices including time of first feed, the type of feeds, starting volumes and advancement rates as well as use of supplements were also sought.

Statistical Analysis

Data were entered on an Excel spreadsheet which was then transferred to Stata 15 (StataCorp, College Station, Texas, USA) for statistical analysis. Summary statistics were calculated: frequencies, means with standard deviation (SD) for normally distributed data and medians with interquartile ranges (IQR) for non-parametric data.

RESULTS

A total of 152 questionnaires were sent out, 48 in Nigeria and 104 in Kenya. A total of 50 were returned representing 37 (74.0%) different hospitals in Nigeria and 13 (26.0%) in Kenya. **Table 1** shows the distribution of the centers according to level of health care provided.

Available Personnel and Services Provided

Neonatal unit size ranged from 2 to 58 cots/incubators; median capacity was 22 (IQR 11–32). All but 2 of the hospitals had neonatologists or pediatricians. The median number of combined neonatologists/pediatricians attending each unit was 9.0 (IQR 3.5–18.0); the median was 10.0 (IQR 4.0–20.0) in Nigeria and 5.0 (IQR 2.5–8.5) in Kenya. **Table 2** shows the level of care, equipment, and services available in the neonatal units across both countries. There were few hospitals with functioning equipment for respiratory support: CPAP machines (22%) and ventilators (8%). Only 31/50 (62%) hospitals reported availability of amino acid preparations for parenteral nutrition. Kangaroo mother care was used in all the Kenyan hospitals in the survey and in 86% of the Nigerian hospitals.

Spectrum of Neonates Treated in the Units

Thirty-nine (78.0%) units accepted babies born at home (outborn) for admission into the same ward and inborns; the remainder admitted outborns to a separate area such as the general pediatric ward. **Figure 1** shows the reported number of babies admitted per month according to birthweight category. Babies with birthweight <1,500 g constituted around a third of all neonatal admissions (median 33.3%; IQR 20–44%). The median number of infants with birthweight <1,500 g admitted per center per month in both countries was 12.0 (IQR 4.8–18.0). Forty-seven centers (94.0%) used postnatal clinical scoring systems such as Dubowitz and Ballard for gestational age assessment. There were no responses on the proportion of mothers with access to early (first trimester) ultrasound scans in pregnancy from the Kenyan units; in Nigeria, 40% were reported to have had access to early ultrasound scans.

TABLE 1 | Level of neonatal care where participants worked by country.

	No of Units		Total
	Nigeria	Kenya	
Secondary level	8	12	20
Tertiary level	29	1	30
Total	37	13	50

Feeding Practices and Clinical Guidelines for Very Preterm and VLBW Babies

Written feeding guidelines for very preterm/VLBW infants were available in 17 (45.9%) of the Nigerian units and 11 (84.6%) of the Kenyan units. All respondents reported initiating enteral feeds with expressed breastmilk. Feeding practices are shown in **Table 3** below. The median volume of advancement of feeds was 20 ml/kg/day (IQR 10–20). The median time to full enteral feeds (defined in the questionnaire as 120 ml/kg/day) was 8 days (IQR 6–12) and the range was from 3 to 20 days. Routine assessment of gastric residual volume before tube feeding was practiced in 39/50 (78.0%) centers. 36 (72.0%) respondents reported that enteral feeds are withheld from babies at key times depending on gestational age, asphyxia, or severe intrauterine growth restriction.

Support for Enteral Feeds

Only 3 (6.0%) practiced buccal colostrum when babies were not yet feeding by mouth and one center in Nigeria used probiotics in VLBW infants. Fortification of breastmilk was practiced in 7 (14.0%) of the units (4 in Nigeria and 3 in Kenya); none of the units had access to donor breastmilk but 12 of the 37 (32.4%) units in Nigeria engaged wet nurses when there was a shortfall in maternal breastmilk supply. None of the Kenyan units reported wet nursing. The majority of respondents, (30; 60.0%)

TABLE 2 | Level of care, investigations, equipment, and services available in the neonatal units.

	Nigeria (*N* = 37) *n* (%)	Kenya (*N* = 13) *n* (%)	Both countries (*N* = 50) *n* (%)
Equipment/consumables Available			
Functioning ventilator(s)	2 (5.4)	2 (15.4)	4 (8.0)
Functioning Continuous Positive Airway Pressure (CPAP) machine(s)	3 (8.1)	8 (61.5)	11 (22.0)
Appropriately sized intravenous cannulas	27 (73.0)	9 (69.2)	36 (72.0)
Peripheral long lines	17 (45.9)	1 (7.7)	18 (36.0)
Umbilical venous catheters	26 (70.3)	4 (30.8)	30 (60.0)
Umbilical artery catheters	8 (21.6)	0 (0.0)	8 (16.0)
Supplemental parenteral nutrition (amino- acids only)	25 (67.6)	6 (46.2)	31 (62.0)
Investigative Capacity			
Microbiology laboratories	34 (91.9)	10 (76.9)	44 (88.0)
X-ray machines	35 (94.6)	13 (100.0)	48 (96.0)
Ultrasonography	33 (89.2)	9 (69.2)	42 (84.0)
Other Services			
Kangaroo Mother Care (KMC)	32 (86.5)	13 (100.0)	45 (90.0)

n, number of facilities.

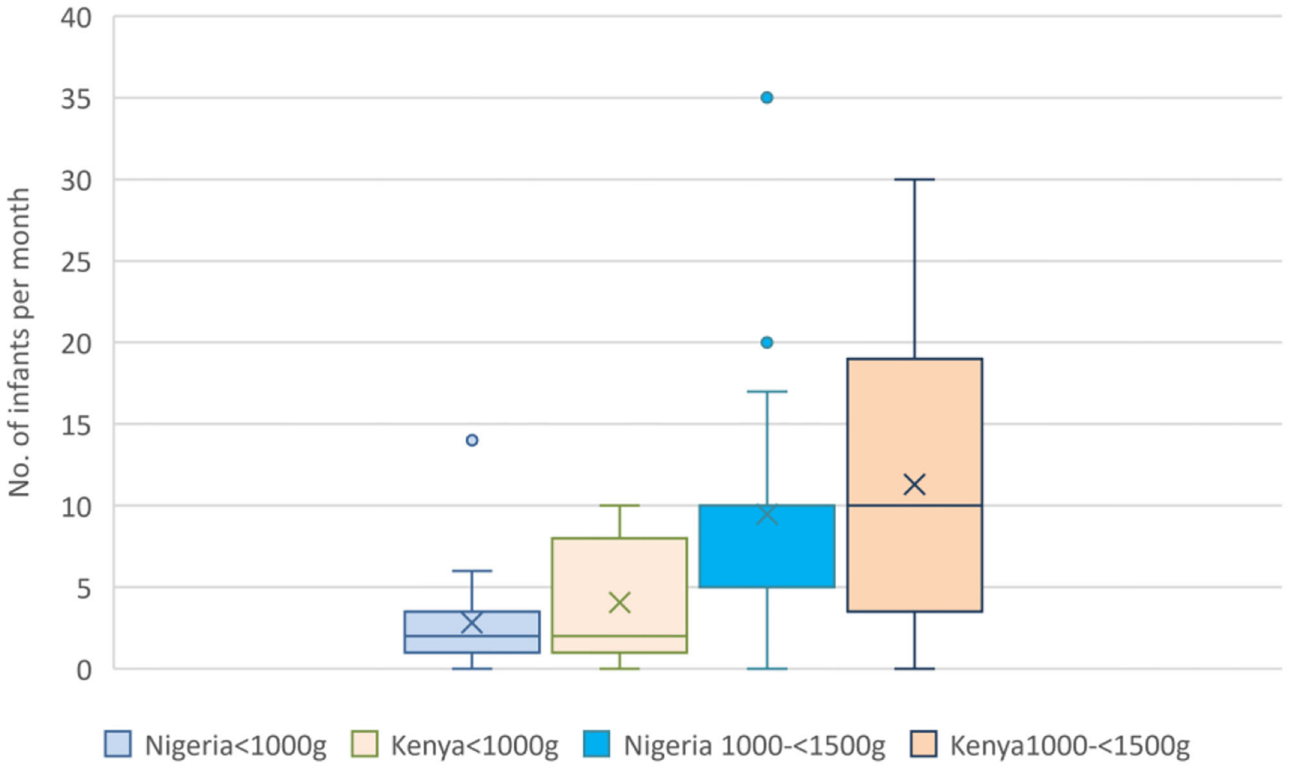

FIGURE 1 | Reported number of admissions of very low birthweight infants per month. Boxes show the IQR with solid line marking the median; X marks the mean; whiskers mark "minimum" (1st quartile-1.5 IQR) and "maximum" (3rd quartile +1.5 IQR) values; dots show outliers.

used formula for top-up feeds. Only 18 (36.0%) of the units had storage facilities for expressed breast milk.

Nutritional supplements given were folic acid in 42 (84.0%) units, iron in 36 (72.0%), calcium in 22 (44.0%) and phosphorus in 5 (10.0%). Vitamin supplements were more often reported in units in Kenya (100.0%) than Nigeria (70.0%).

DISCUSSION

This survey of enteral feeding practices for very preterm and/or VLBW babies at secondary and tertiary levels of health care in Nigeria and Kenya shows very wide variations in practice within and between both countries. Although all of the units initiated feeds using expressed breast milk, only about half initiate feeding within the first 24 h and some not until after 72 h. This marked variability in practice likely accounts for the equally marked variation between units in time to reach full feeds.

Most units routinely checked gastric residual volume before oral and/or nasal tube feeding. Other modes of feeding utilized were cup, cup and spoon, and bottle. None of the units had access to donor breast milk. Formula feeds, breast milk fortifiers and wet nurses (in Nigeria only) were used to supplement shortfalls in expressed breast milk. In addition, probiotics, and nutritional supplements (folic acid, iron, calcium, and phosphorus) were widely administered. Few of the units used buccal colostrum.

Written feeding guidelines were in use in 45.9 and 85.6% of the Nigerian and Kenyan units, respectively. The use of standardized feeding protocols in middle and high income countries (18–20), is associated with earlier achievement of full enteral feeds (thus shorter use of vascular catheters), and reduced rates of neonatal sepsis, NEC, extrauterine growth restriction, and overall, decreased length of stay in the hospital. However, variations in feeding practices across units also occur in high income countries depending on a number of factors including access to facilities such as breastmilk banks (21, 22). Currently there is little research on preterm feeding practices in sSA to inform feeding protocols for these at-risk infants (13). Kenya has a national guideline for feeding these vulnerable infants (23). In Nigeria, guidelines for comprehensive newborn care in secondary and tertiary hospitals were launched on 25th November, 2021 (24). This occurred after this survey was done, thus less than half of the centers in Nigeria had unit protocols for preterm feeding. Though this study did not evaluate the degree to which facilities adhered to their protocols, it has highlighted strengths and opportunities to build on as well weaknesses and threats or challenges to address in order to successfully implement a national guideline or protocol. The implementation of national guidelines would present an opportunity for evaluation and comparison of preterm feeding across a large number of neonatal units.

TABLE 3 | Reported feeding practices.

	Nigeria (*N* = 37) *n* (%)	Kenya (*N* = 13) *n* (%)	Both countries (*N* = 50) *n* (%)
Time to first feed			
Within first 24 h of life	16 (43.2)	8 (61.5)	24 (48.0)
>24 to 48 h of life	12 (32.4)	3 (23.1)	15 (30.0)
>48 h to 72 h of life	7 (18.9)	2 (15.4)	9 (18.0)
>72 h of life	2 (5.4)	0 (0.0)	2 (4.0)
Starting volume of feeds			
10–20 ml/kg/day	34 (91.9)	2 (15.4)	36 (72.0)
40–80 ml/kg/day	3 (8.1)	11 (84.6)	14 (28.0)
Volume of advancement of feeds			
Less than 10 ml/kg/day	1 (2.7)	1 (7.7)	2 (4.0)
10–20 ml/kg/day	31 (83.8)	11 (84.6)	42 (84.0)
More than 20 ml/kg/day	4 (10.8)	1 (7.7)	5 (10.0)
Frequency of feeds			
Continuous	4 (10.8)	0 (0.0)	4 (8.0)
1 hourly	2 (5.4)	0 (0.0)	2 (4.0)
2 hourly	26 (70.3)	0 (0.0)	26 (52.0)
3 hourly	12 (32.4)	13 (100.0)	25 (50.0)
4 hourly	4 (10.8)	0 (0.0)	4 (8.0)
Mode of feeding			
Nasogastric tube only	20 (54.1)	8 (61.5)	28 (56.0)
Orogastric tube only	7 (18.9)	0 (0.0)	7 (14.0)
Nasogastric and orogastric tube	8 (21.6)	3 (23.1)	11 (22.0)
Cup	26 (70.3)	10 (76.9)	36 (72.0)
Cup and spoon	11 (29.7)	4 (30.8)	15 (30.0)
Bottle	2(5.4)	1 (7.7)	3 (6.0)

The overall aim of feeding guidelines/protocols for these at-risk infants is to achieve full enteral feeds in the shortest possible time and safely, to promote immediate and long-term health. An overview of systematic reviews of feeding practices for VLBW infants in sSA (13) showed research gaps related to optimal time to starting feeds, what to feed, what volume to start with, how to advance, best mode of feeding and what supplements to use. All these practices must take into account what facilities and support are available and sustainable particularly in systems where care is paid for out of pocket.

Few units practiced administration of buccal or oropharyngeal colostrum despite this being a low-cost procedure that is being increasingly adopted in high income settings with the potential to reduce time to full enteral feeds (25). This may reflect the length of time needed for research findings to be incorporated into clinical guidelines and routine practice, the first publication dating from 2009 (26). Most units started enteral feeding with trophic feeds ranging between 10 and 20 ml/kg/day, with daily advancements of 10–20 ml/kg/day, though there is evidence from developed countries that faster advancement of 30–40 ml/kg/day may be safe and facilitates earlier attainment of full enteral feeds (8, 27) few of the units in this survey advanced more than 20 ml/kg/day. The WHO feeding guidelines for preterm infants recommend a daily increase "up to" 30 ml/kg for LMICs (14) and this may be the reason for the observed practice. The fact that the clinical status of the infants in sSA and the level of monitoring and nursing care might not be similar to those in high income countries, coupled with the suboptimal nutritional, economic and overall conditions of mothers as well as the health system set up (28) may all intricately interact to interfere with lactation, milk expression and storage and feeding regimens in these units. The WHO recommendation needs to be evaluated for infants in this region.

Multicentre studies in Africa need to factor in the particular challenges with resources such as donor breastmilk banks, with evaluation of different implementation models such as in South Africa (23). The first human breastmilk bank in Kenya commenced in Nairobi in 2019 with a view to scaling up. This process took 3 years from planning to eventual inauguration (29). No donor milk bank exists in Nigeria which may be related to resource constraints and/or cultural and religious factors. Some centers, however, utilized wet nursing to provide breastmilk. It will be informative to conduct research into the cultural acceptability and extent of this practice as well as safety particularly in the context of novel and evolving infectious diseases, as this may prove a useful and affordable alternative to breastmilk banking.

Limitations

This study had a number of limitations. Convenience sampling was used, and the number of respondents was low, particularly from Kenya. Therefore, the findings may not be entirely representative of feeding practices in neonatal units in Nigeria and Kenya. In addition, feeding practices were self-reported and not verified from hospital records. Another limitation lies in the fact that the view of the most senior doctor in each unit was used hence it may reflect more of the intentions rather than the actual practice of junior doctors, nurses, and nutritionists involved in day-to-day decisions on feeding practices, especially in centers where there are no written feeding guidelines. Information from nurses and parents was not collected. Despite these limitations, the survey provides data from two different sSA countries to generate key context-relevant research questions.

CONCLUSION

Feeding practices in very preterm/VLBW infants vary widely in Nigeria and Kenya possibly due to a complete lack of locally generated evidence to guide practice. High quality research into feeding of very preterm/VLBW infants, that is sensitive to the context of limited human resources, technology, and consumables, is urgently needed to inform the development of guidelines appropriate to these settings.

NEONATAL NUTRITION NETWORK MEMBERS

Isa Abdulkadir (Ahmadu Bello University, Zaria, Nigeria); Ismaela Abubakar (Liverpool School of Tropical Medicine, Liverpool, UK); Abimbola E. Akindolire (College of Medicine, University of Ibadan, Nigeria); Olusegun Akinyinka (College of Medicine, University of Ibadan, Nigeria); Stephen J. Allen (Liverpool School of Tropical Medicine, Liverpool, UK); Pauline E. A. Andang'o (Maseno University, Kenya); Graham Devereux (Liverpool School of Tropical Medicine, Liverpool, UK); Chinyere Ezeaka (College of Medicine, University of Lagos/Lagos University Teaching Hospital, Nigeria); Beatrice N. Ezenwa (College of Medicine, University of Lagos/ Lagos University Teaching Hospital, Nigeria); Iretiola B. Fajolu (College of Medicine, University of Lagos/ Lagos University Teaching Hospital, Nigeria); Zainab O. Imam (Lagos State University Teaching Hospital, Lagos, Nigeria); Kevin Mortimer (Liverpool School of Tropical Medicine, Liverpool, UK); Martha K. Mwangome (KEMRI Wellcome Trust Research Programme, Kilifi, Kenya); Helen M. Nabwera (Liverpool School of Tropical Medicine, Liverpool, UK); Grace M. Nalwa (Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu, Kenya & Maseno University, Kenya); Walter Otieno (Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu, Kenya & Maseno University, Kenya); Macrine A. Olwala (Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu, Kenya); Alison W. Talbert (KEMRI Wellcome Trust Research Programme, Kilifi, Kenya); Nicholas D. Embleton (Newcastle University, Newcastle, UK); Olukemi O. Tongo (College of Medicine, University of Ibadan, Nigeria); Dominic D. Umoru (Maitama District Hospital, Abuja, Nigeria); Janneke van de Wijgert (University of Liverpool, Liverpool, UK); Melissa Gladstone (University of Liverpool, Liverpool, UK).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

OT contributed to conception and design of the study and the first draft of the manuscript. MO and AT were co-authors. All authors contributed to manuscript revision, read, and approved the submitted version.

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BRIEF RESEARCH REPORT
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Neurodevelopmental Outcomes of Extremely Low Birth Weight Survivors in Johannesburg, South Africa

Tanusha D. Ramdin[1,2], Robin T. Saggers[1,2], Rossella M. Bandini[2], Yoliswa Magadla[1,2], Aripfani V. Mphaphuli[1,2] and Daynia E. Ballot[2]*

[1] Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [2] PRINCE (Project to Improve Neonatal Care), School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa

Background: Improved survival in extremely low birth weight infants (ELBWI) in Sub-Saharan Africa has raised the question whether these survivors have an increased chance of adverse neurodevelopmental outcomes.

Objectives: To describe neurodevelopmental outcomes of ELBWI in a neonatal unit in South Africa.

Methods: This was a prospective follow-up study. All ELBWI who survived to discharge between 1 July 2013 and 31 December 2017 were invited to attend the clinic. Bayley Scales of Infant and Toddler Development (version III) were conducted at 9 to 12 months and 18 to 24 months.

Results: There were 723 ELBWI admissions during the study period, 292 (40.4%) survived to hospital discharge and 85/292 (29.1%) attended the neonatal follow up clinic. The mean birth weight was 857.7 g (95% CI: 838.2–877.2) and the mean gestational age was 27.5 weeks (95% CI 27.1–27.9). None of the infants had any major complication of prematurity. A total of 76/85 (89.4%) of the infants had a Bayley-III assessment at a mean corrected age of 17.21 months (95% CI: 16.2–18.3). The mean composite scores for cognition were 98.4 (95% CI 95.1–101.7), language 89.9 (95% CI 87.3–92.5) and motor 97.6 (95% CI 94.5–100.6). All mean scores fell within the normal range, The study found 28 (36.8%) infants to be "*at risk*" for neurodevelopmental delay.

Conclusion: Our study demonstrates good neurodevelopmental outcome in a small group of surviving ELBWI, but these results must be interpreted in the context of the high mortality in this group of infants.

Keywords: extreme low birth weight infants, neurodevelopmental, Sub-Saharan Africa, intensive care, Bayley Scales of Infant and Toddler Development-third edition

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Karim Premji Manji,
Muhimbili University of Health and Allied Sciences, Tanzania

****Correspondence:***
Tanusha D. Ramdin
tanusha.ramdin@wits.ac.za

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BACKGROUND

In South Africa, preterm birth occurs in ∼15% of all births–that is, one in seven infants are born premature (1, 2). Extremely low birth weight infants (ELBWI) are defined as having a birth-weight <1,000 g. Fortunately, advances in neonatal care over the last few decades have improved the survival of premature infants, raising concerns about their morbidity and neurodevelopmental outcomes (3).

The World Health Organization (WHO) reported that three quarters of premature infants can be saved with feasible and cost-effective care, such as antenatal steroids, kangaroo mother care and breastfeeding (1, 2). Yet, there is a notable difference in the rates of survival and neurodevelopmental impairment in ELBWI in high income countries (HICs) compared to low and middle income countries (LMICs). In HICs, the mortality rate of extremely premature infants is <10%, compared to 70–90% in LMICs (3, 6). These differences are attributed to several factors; namely population demographics, antenatal and neonatal care, post-hospital discharge guidelines and resource availability (4).

Decreasing mortality rates in ELBWI in LMICs by establishing a high level neonatal intensive care unit (NICU) might incur a huge financial burden as well as risk of inequity and diverting resources from more mature neonates. However, a study conducted by Ballot et al. (5) at a tertiary hospital in Johannesburg, showed an improved survival rate of 50% between 2006/2007 and 2013 by giving surfactant and nasal continuous positive airway pressure (NCPAP) to infants between 750 and 900 g. Similarly, a study in Cape Town, reported an increased survival of 75% in infants with a birthweight 500–1,000 g who received NCPAP and surfactant therapy (6). This highlights that simple, low-cost interventions provided to ELBWI can significantly improve survival rates.

Survivors may experience a range of short term morbidities including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular haemorrhage (IVH) and long term neurodevelopmental morbidities, which may include developmental delay, cerebral palsy, blindness, and deafness (7–9). A literature review by Jarjour et al. (7) concluded that nearly half of surviving ELBWI will have significant neurodevelopmental disability on short and long term follow up.

In LMICs there is very limited data on long term neurodevelopmental outcomes of ELBWI (10). Ballot et al. (11) conducted a study in a similar setting in 2013 assessing neurodevelopmental outcomes in very low birth weight infants (VLBWI) using the Bayley Scales of Infant and Toddler Development III (Bayley-III), in which a subset of ELBWI had no evidence of developmental delay. This was in agreement with reports of good developmental outcomes of ELBWI in India, a low income country (12). A Cochrane review by Spittle et al. (13) of 25 randomized trials indicated that early neurodevelopmental interventions, like parent-infant interactions and physiotherapy interventions based on principles of neuro-developmental therapy, has benefits for preterm infants in combined cognitive and motor outcomes.

This study aimed to determine the neurodevelopmental outcome of ELBWI in a middle income country in Sub-Saharan Africa.

METHODS

This was a prospective follow-up study of ELBWI born between 1 July 2013 and 31 December 2017. The study was conducted at the neonatal unit of a tertiary hospital in Johannesburg, South Africa. Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a public sector hospital that serves a low socioeconomic community that does not have access to private health insurance All ELBWI who survived to hospital discharge were invited to enrol. Enrolment was done at the first clinic visit.

The ELBWI study group were seen at the study clinic every 3 months until the corrected age of 24 months. To improve rates of follow-up, text messages were sent to parents of enrolled participants as reminders of follow-up appointments. Transport costs were refunded and defaulting patients were traced and rebooked where possible.

Appropriately trained paediatricians and physiotherapist performed the developmental assessments using the Bayley Scales of Infant and Toddler Development, version III (Bayley-III) (11). The Bayley III was validated in the same setting (14). The first Bayley-III assessment was conducted between 9 and 12 months; the second between 18 and 24 months (if patient still attended the follow up clinic). The Bayley-III assessment would be done at the next visit if a child defaulted a study clinic visit. The Bayley-III scores were calculated using the age corrected for prematurity. The gestational age was assessed by maternal menstrual history and clinical assessment using the Ballard score (11). The Cronbach's alpha interclass correlation between different observers for neurodevelopment assessment was 0.89 (14). Infants with congenital abnormalities that were likely to affect neurodevelopment, for example Trisomy 21, were subsequently excluded from the study.

Developmental delay was classified *"at risk"* if a composite Bayley-III score was below 85 on any of the cognitive, language or motor sub-scales and as *"delayed"* if a composite Bayley-III score was below 70 on any of the sub-scales (14). Cerebral palsy was diagnosed if there was a delay in motor milestones together with abnormal movement and/or posture (14). Hearing and vision were indirectly assessed as part of the Bayley-III language and motor assessment. Where developmental problems were identified, the child was referred for appropriate intervention by the allied medicine team (physiotherapy, occupational therapy and speech therapy).

Data Management

Data were entered and managed using Research Electronic Data Capture (REDCap™) software, hosted by the University of Witwatersrand (15). Maternal variables included demographics, antenatal care (ANC), obstetric history, place and mode of delivery. Neonatal variables included gestational age, birth weight, sex, duration of ventilation and stay, neonatal morbidity, late sepsis and outcome.

Statistical Analysis

The data were exported into SPSS version 23 (IBM, USA) for statistical analysis. The latest Bayley-III score for each child was used for analysis. The composite cognitive, language and motor scores were used as outcome variables. If continuous variables were normally distributed, the data was described using mean and 95% confidence intervals (95% CI). Skewed data was described using median and interquartile range (IQR). Categorical variables were described using frequency and percentages. Survivors and non-survivors were compared–continuous variables were compared using unpaired *t* test or Mann Whitney U depending on the data distribution. Categorical variables were compared using Chi Square. Only valid cases were analysed for each variable (i.e., missing data was excluded).

Ethical Considerations

Written informed consent was obtained from the parents of each participant prior to study enrolment. The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, approved the study (reference numbers M120623 & M170702).

RESULTS

There were 723 ELBWI admitted to the unit during the study period. The characteristics of survivors and non-survivors is shown in **Table 1**. The overall cohort of ELBWI had a mean birth weight of 822.28 grams and gestational age of 27.09 weeks. The majority of ELBWI received NCPAP (74.6%). ELBWI who died were of lower birth weight and gestational age and more likely to have complications of prematurity (**Table 1**). Patient selection is shown in **Figure 1**. Of 292 infants who were discharged, 85 (29.1%) attended the follow-up clinic.

Neurodevelopmental assessment was conducted in 76 of the 85 (89,4%) infants who attended the clinic. The characteristics of these infants are shown in **Table 2**.

The Bayley-III assessment was conducted at a mean corrected age of 17.21 months (95% CI: 16.2–18.3). The mean composite scores are shown in **Table 3**. All mean scores fell within the normal range, but the composite language score was the lowest. We did not diagnose cerebral palsy in any of the infants. These findings were similar to the neurodevelopmental outcomes in a group of low risk term infants from the same unit (11) (see **Table 3**).

We found 28 of 76 ELBWI infants (36.8%) infants to be "*at risk*"—17 in one domain; seven in two domains and four in three domains. The language domain had the most "*at risk*" infants, with 22 of 76 infants at risk. Of the 28 "*at risk*" infants, we

TABLE 1 | Clinical characteristics and risk factors associated with mortality in ELBWI at a tertiary hospital in Johannesburg, South Africa.

	Total *N* = 723	Died *N* = 409	Survived *N* = 314	*P*-value
Birthweight (grams)	822.28 ± 103.7 Median and IQR	771.11 ± 125.2 Median and IQR	873.45 ± 82.2 Median and IQR	***P* < 0.001**
Gestational age (Weeks)	27.09 ± 2.01 Mean and SD	26.48 ± 2.17 Mean and SD	27.7 ± 1.86 Mean and SD	***P* = 0.014**
Late onset sepsis	260 (36.0%)	101/409 (24.7%)	159/314 (50.6%)	***P* < 0.001**
Intraventricular haemorrhage grade 3 or 4	44 (6.1%)	31/409 (7.6%)	13/314 (4.1%)	*P* = 0.06
Patent ductus arteriosus	89 (12.3%)	34/409 (8.3%)	55/314 (17.5%)	***P* < 0.001**
Necrotising enterocolitis	55 (7.6%)	30/409 (7.3%)	25 / 314 (8.0%)	*P* = 0.778
Gender = male	313 (43.3%)	183/409 (44.7%)	130/314 (41.4%)	*P* = 0.405
5 min Apgar 5 or less	133 (18.4%)	96/364 (26.3%)	37/288 (12.8%)	***P* < 0.001**
Nasal continuous positive airways pressure	531 (74.6%)	281/409 (68.7)	258/314 (82.2%)	***P* < 0.001**

IQR, Interquartile Range; SD, Standard deviation. Bold values indicate the significant variables.

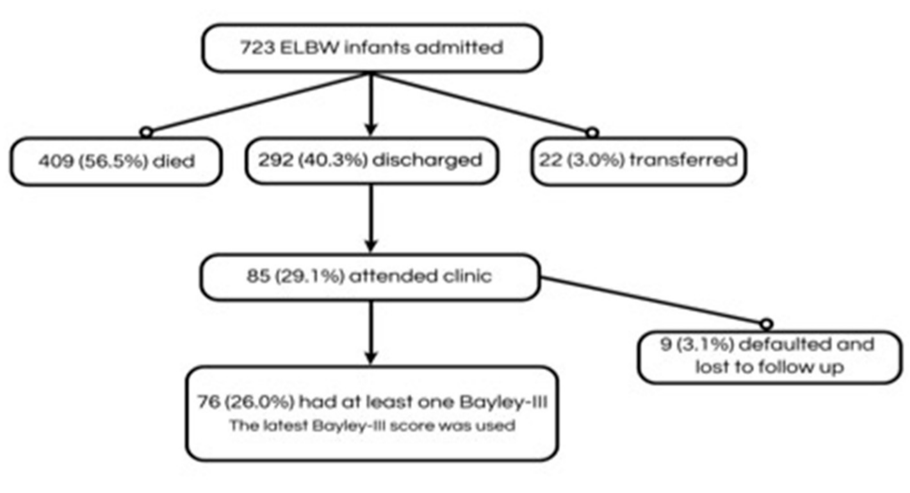

FIGURE 1 | Participants included in the study of neurodevelopmental outcomes of extremely low birth weight infants at a tertiary hospital in Johannesburg, South Africa, 1 July 2013 and 31 December 2017.

classified two (2.6%) as disabled–one in all three domains and one in two domains (motor and language). There were no cases of cerebral palsy identified.

DISCUSSION

Our study provides information on neurodevelopmental outcomes of ELBWI in a middle- income country (MIC) in Sub Saharan Africa. The mean cognitive, language and motor Bayley-III scores were all within the normal range and there were no cases of cerebral palsy. The neurodevelopmental outcome of the ELBWI was similar to that in a group of low-risk term infants from the same setting (11). These findings are encouraging and provide evidence that some ELBWI in Sub Saharan Africa can have a normal outcome. This type of information is useful to inform neonatal protocols and parental counseling in this context.

Importantly, more than one third of the ELBWI were identified as "*at risk*" and two of them were disabled. There were no disabled infants and 25.6% with cognitive delay, 16.2% language delay and 5.2% motor delay in the group of low-risk term infants from the same setting (11). The identification of at risk and disabled infants enabled the early referral to rehabilitation services. Appropriate early neurodevelopmental intervention may assist in decreasing the burden of a lifetime of functional disability after preterm birth (13). Ideally ELBWI require longer follow up to the age of 8 years or more to discover more unfolding sequalae.

TABLE 2 | Clinical and demographic characteristics of 76 extremely low birth weight infants assessed with Bayley Scales of Infant and Toddler Development (Version III) at a tertiary hospital in Johannesburg, South Africa.

Variable	Frequency	Percentage
Maternal characteristics		
Antenatal care (at least one visit)	68	89·5
Antenatal steroids (any number of doses)	46	60·5
Antenatal magnesium sulphate for preeclampsia	10	13·2
Maternal hypertension	33	43·4
Maternal HIV	20	26·3
Chorioamnionitis	1	1·3
Mode of delivery		
Delivered by elective or emergency caesarean section	55	72·3
Neonatal characteristics		
Resuscitation at birth	38	50·0
Five minute Apgar score below 6	10	13·1
Respiratory distress syndrome	74	97·4
Surfactant therapy	62	81·6
Nasal CPAP without mechanical ventilation	48	63·2
Mechanical ventilation	13	17·1
Early onset sepsis (<72 h of life)	2	2·6
Complications of prematurity		
Patent ductus arteriosus	9	11·8
Necrotising enterocolitis stage 2 or 3	4	5·3
Anaemia requiring blood transfusion	56	73·7
Late onset sepsis (>72 h of life)	36	47·4
Intraventricular haemorrhage Grade 1 or 2	14	18·4
Steroids for chronic lung disease	27	35·5
Retinopathy of prematurity stage 3 or more	1	1·3
Outcomes		
Kangaroo mother care	48	63.2
Exclusively breastfed on discharge	32	42.1

Cautious Interpretation

These promising results must be interpreted with caution. There is strong selection bias in this study due to the high mortality in this group of high-risk infants. The normal developmental outcome in our study is in strong contrast to report rates of handicap in ELBWI in HICs (16). However, none of the surviving ELBWI in our study had any serious complication of prematurity and would be expected to have a normal outcome. Previous research in our unit has shown a strong association between complications of prematurity and mortality (17). The smallest and sickest babies do not survive to discharge. Our survival rate of ELBWI 40% is less than half that reported in HICs but similar to other MICs (3, 6). Therefore, our study evaluated a group of good survivors who may be expected to have normal development.

We also had a low rate of follow up in our study. Only one third of the ELBWI survivors attended the follow up clinic. We did not evaluate reasons for failing to attend the follow up clinic, but these may include financial issues, lack of transport, relocation to other provinces or countries and parents unable to miss work to attend the clinic. Unfortunately, we do not know the developmental outcome of the infants that were lost to follow-up.

TABLE 3 | Composite score of Bayley Scales of Infant and Toddler Development (Version III) in 76 extremely low birth weight and low-risk term infants at a tertiary hospital in Johannesburg, South Africa.

	Extremely low birth weight infants		Low risk term infants	
Domain	**Mean composite score**	**95% Confidence intervals**	**Mean composite score**	**95% Confidence intervals**
Cognitive	98·4	95·1–101·7	92.2	89.4–95.0
Language	89·9	87·3–92·5	94.8	92.5–97.1
Motor	97·6	94·5–100·6	98.8	96.8–101.0

Study Limitations

Imprecise gestational age determination was a limitation of the study. The gestational age was based on a Ballard assessment in most cases and not accurate dates, nor first trimester antenatal sonar. Access to first trimester antenatal sonar is very limited in our setting. Most mothers present to antenatal clinic book during second or third trimester of pregnancy. Second and third trimester accuracy in determining gestational age varies from 10 to 30 days, respectively. Mothers usually present late in labour to the hospital. Therefore, in our setting birth weight is routinely used instead of gestational age (11, 18).

The high loss to follow up of neonatal survivors is a challenge in our setting. We did not evaluate the reasons for loss to follow up but CMJAH is a tertiary hospital in the inner city of Johannesburg. The low rate of follow up could be related to the migrant population. More than one third of the CMJAH mothers come from neighboring provinces or countries to give birth at CMJAH and return homes after their babies are discharged. Many mothers return to work, and it is extremely difficult for them to take off from work to the attend clinic. Due to limited financial resources, there is no dedicated social worker or nurse to ensure that babies return to follow up clinic.

The ELBWI survivors in our study were treated in a specialised tertiary centre and are therefore not generalizable to lower levels of care. Most ELBWI are born and treated in regional and district hospitals without the same level of neonatal care.

So too there are limitations on the assessment tools used: the Bayley-III may underestimate impairment among extremely preterm infants (19). Studies have found that the mean score of cognitive and motor development was close to normal (means 96.9–100.4), which is higher than expected when compared to the prior data of similar cohorts tested with Bayley-II (11). Furthermore, the infants' first or home language are not English therefore the composite language scores may have been lower than expected and relatively lower than other composite scores. However, the language score was low but within normal limits. Low language score was also found in similar studies done at our settings (11). Cranial ultrasound of the study group showed grade 1 and 2 IVH and is unlikely to be associated with low language score.

CONCLUSION

Although these results are encouraging, there is strong selection bias in our study sample. The survival rate of ELBWI was low, the surviving infants did not have major complications of prematurity and most survivors did not attend neonatal follow up clinic. Our results show that this small sub-group of ELBWI had normal developmental outcomes at approximately 24 months but does not reflect neurodevelopmental outcome in all ELBWI in sub-Saharan Africa.

The study also demonstrated some of the significant challenges relating to this type of follow up in LMICs. Our results highlight the need for a properly resourced prospective cohort follow up study of ELBWI in LMICs, to have reliable neurodevelopmental outcome data in this group of vulnerable infants. Understanding these outcomes of prematurity will provide important data to neonatologists, treating doctors, families and policy makers and will guide decision making regarding the provision of intensive care for ELBWI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, (reference numbers M120623 and M170702). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TR performed data collection and wrote up the various drafts for publication. DB conceptualized the study, performed data collection and analysis, assisted in the write up, and review of the various drafts for publication. RS, YM, AM, and RB assisted with data collection. RS and RB assisted in the review of the final draft for publication. All authors have read and approved the final version of this manuscript.

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Neonatal Mortality Rate and Its Determinants: A Community–Based Panel Study in Ethiopia

Kasiye Shiferaw[1*], *Bezatu Mengistie*[2], *Tesfaye Gobena*[3], *Merga Dheresa*[1] and *Assefa Seme*[4]

[1] *School of Nursing and Midwifery, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia,* [2] *School of Public Health, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia,* [3] *Department of Environmental Health Science, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia,* [4] *School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia*

Background: The Sustainable Development Goals specifically target a reduction in neonatal mortality rates. However, the highest neonatal mortality rates occur in sub-Saharan Africa, including Ethiopia. Although several factors contributing to these high rates have been explored, there continues to be a general dearth of studies and inconsistencies of factors to understand the problem. Therefore, this study aimed to identify the prevalence and factors associated with neonatal mortality in Ethiopia.

Methods: A panel study was conducted among 2,855 pregnant or recently postpartum women selected using the multistage cluster sampling technique from October 2019 to September 2020. Data were collected by experienced and trained female resident enumerators and coded, cleaned, and analyzed using STATA version 16.1 software. We used the Kaplan–Meier survival curve to show the pattern of neonatal deaths during the first 28 days of life. Frequencies and rates were reported along with the percentages and using a 95% confidence interval, respectively. The Cox proportional hazard regression model was used to explore the association of explanatory and outcome variables. Finally, an adjusted hazard ratio with a 95% confidence interval was used to report the results, with a $p < 0.05$ to declare statistical significance.

Results: The neonatal mortality rate was 26.84 (95% CI: 19.43, 36.96) per 1,000 live births. Neonates born to rural resident mothers (AHR = 2.18, 95% CI: 1.05, 4.54), mothers of advanced age (AHR = 2.49, 95% CI: 1.19, 5.21), and primipara mothers (AHR = 3.16, 95% CI: 1.52, 6.60) had a higher hazard of neonatal mortality. However, neonates born to women who attended technical and vocational level education (AHR = 0.08, 95% CI: 0.01, 0.62) had a lower hazard of neonatal mortality.

Conclusions: The neonatal mortality rate in Ethiopia is high, with increased risk among specific subsets of the population. The findings highlight that neonatal survival can be improved through tailored interventions for rural residents, emerging regions, and primipara women by improving female education and avoiding pregnancy at an advanced maternal age to achieve Sustainable Development Goal target 3.2.

Keywords: survival, prevalence, neonate, predictors, Ethiopia

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Andrew Steenhoff,
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United States

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Drucilla Jane Roberts,
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United States
Greg Valentine,
University of Washington,
United States

***Correspondence:**
Kasiye Shiferaw
sifkas.gem2@gmail.com

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BACKGROUND

The Sustainable Development Goal (SDG) 3.2 targets to reduce neonatal mortality (NM) to 12 deaths per 1,000 live births or lower by 2030; however, accelerated progress is needed by countries to reach this goal (1, 2). Neonatal mortality is death among neonates during the first 28 days of life after a live birth (3). The first month is critical for newborn survival (4). Since neonatal mortality contributes to the majority of under-5 mortality, it is a relevant indicator of children's wellbeing and health (1). The global neonatal mortality decreased from 5 to 2.5 million from 1990 to 2017; however, the annual NM rate fluctuates. The NM rate was 27 per 1,000 live births in sub-Saharan Africa (SSA) (4) and 30 per 1,000 live births in Ethiopia, with slight improvement (5, 6).

Sociodemographic factors, reproductive health, perinatal care, and child-feeding practice contribute to the high NM rate (4, 7, 8). Specifically, the women's level of education (9–11), place of residence (9, 12, 13), parity (14, 15), delivery place (10), newborn age (16), women's age (16–18), newborn sex (11, 19), gestational age (16), maternal or fetal complications (20, 21), delivery mode (20–22), low birth weight (21, 23, 24), low Apgar score (14, 23), congenital abnormalities (21, 23), late initiation of breastfeeding (16, 19, 20), non-exclusive breastfeeding (16), and inadequate antenatal care (ANC) visits (16, 20, 24) were associated with neonatal mortality across low- and middle-income countries (LMICs).

The pooled NM prevalence in Ethiopia varied from 6.8 (25) to 16.3% (7), which is unacceptably high. Therefore, a continuum of care is recommended to improve neonatal survival (26). Current studies in Ethiopia are limited to specific geographical locations (27, 28) and are primarily facility-based (12, 16, 17, 29–32); hence, it is challenging to estimate NM's national burden and predictors. Additionally, current pieces of evidence on incidence and predictors of NM were limited and at the national level, based on the demographic health survey (DHS), which is subject to recall bias since it depends on the women's recall of the past 5 years (13, 19, 33, 34). Hence, there is a general dearth of studies and inconsistencies in understanding the problems contributing to NM. Therefore, this study aimed to identify the prevalence and factors associated with neonatal mortality in Ethiopia.

MATERIALS AND METHODS

Study Design, Setting, and Period

A panel design was conducted in six regions of Ethiopia, Tigray, Afar, Amhara, Oromia, South Nation Nationalities and People (SNNP), and Addis Ababa city administration. These regions represent ∼90% of the country's total population (35). The study was conducted from October 2019 to September 2020.

Abbreviations: AHR, Adjusted hazard ratio; ANC, antenatal care; CHR, Crude hazard ratio; EDHS, Ethiopian demographic health survey; HCP, health care provider; HEWs, health extension workers; NM, neonatal mortality; NMR, neonatal mortality rate; PNC, postnatal care; SDG, Sustainable Development Goal; TeVT, Technical and vocational training; WHO, world health organization.

Sample Size and Sampling Population

The final sample size in this panel study was 2,855, which was nested within 217 enumeration areas. First, the roster of all households was created in the community to identify eligible females for the panel study during the census. Then, eligible women were identified and enrolled in the panel study using a screening form. The pregnant or recently postpartum (<8 weeks postpartum with a live birth) women living in the panel regions were eligible. In addition, if a woman was staying at her parents' home during the census and screening, she qualified (even though this was not her permanent residence).

Variables

Neonatal mortality was the outcome variable. The women who had a live birth but lost their neonate within the first 28 days postpartum were coded as "1", otherwise, it was considered "0". The explanatory variables included women's age (15–19, 20–24, 25–29, 30–34, $\geq$35 years), place of residence (urban or rural), wealth quintile (lowest, lower, middle, higher, or highest), level of education (never attended, primary, secondary, technical, and vocational or higher), dwelling region (Tigray, Afar, Amhara, Oromia, SNNP, Addis Ababa), religion (Orthodox, Muslim, Protestant, others), marital status (married or others), parity (primipara, multipara), ever been pregnant (yes or no), ANC attendance (yes or no) and sex of neonate (male or female).

Advanced maternal age was defined as women aged 35 and above (36). We calculated the wealth quintile from household assets and housing conditions. Hence, households were given a score based on the number and types of goods and housing characteristics. The principal component analysis derived the scores. The scores were divided into five equal categories (5). Urban was defined as a locality with 2,000 or more inhabitants. However, it also included district capitals, localities with urban dweller associations, and localities primarily engaged in non-agrarian activities with 1,000 or more inhabitants (37). The women's marital status was categorized based on her response to the question 'are you currently married or living together with a man as if married?' The woman's marital status was labeled as "married" if her response was currently married or living with a man, on the other hand, if she responded that she was divorced, separated, widowed, or never married, it was categorized as "others."

Data Collection

The tools were adapted from the demographic health surveys, and previous Performance Monitoring for Action (PMA) Ethiopia tools and developed by reviewing the literature. The tool is available on the PMA website (https://www.pmadata.org/data/survey-methodology). Experienced, trained, female resident enumerators collected the data using an interviewer-administered questionnaire. First, a baseline assessment was conducted following the enrollment of the participants. Then, for baseline data collection, wave two data collection was conducted from 5 to 8 weeks postpartum, both for pregnant or recently postpartum women.

Data Quality Assurance

A validated questionnaire adapted from the demographic health survey tool, previous PMA Ethiopia tool, and reviewing literature were pretested in the Oromia zone; results were excluded in the actual data analysis. Diploma data collectors and supervisors were recruited. The data collectors had varying years of prior experience among themselves. Many participated in the DHS; additionally, some data collectors had worked with the longstanding cross-sectional PMA in Ethiopia (ongoing since 2014) and a similar panel study in SNNP in 2016. Female resident enumerators and supervisors received comprehensive training on data collection tools and procedures for 2 weeks. The consented study participants were repeatedly contacted during round two data collection (i.e., three visits as needed) and provided with an incentive mobile card to minimize loss of follow-up. The data were downloaded from the aggregate server daily and cleaned using STATA version 16.1 software by the data management team.

Data Processing and Analysis

Data were downloaded to STATA version 16.1 software for analysis. Frequency tables and Kaplan–Meier curves were used during descriptive analysis. Unequal clusters and women's probability selection and non-response bias were compensated by sample weights (women and household). The sample weight was the output of inverse household and enumeration areas selection probability, female, and household response rate in this study.

The outcome was a dichotomous variable coded as one when NM occurred within 28 days of delivery after live birth. Otherwise, it was coded as zero. The time to death was calculated by subtracting the birth date from the date of death. The neonatal mortality rate was calculated as neonatal deaths per 1,000 live births. The neonatal mortality rate was described each year with a 95% confidence interval (CI). Kaplan–Meier survival curve was used to show the neonatal death patterns, and a log-rank test was used to compare the survival curves among the independent variables. The variance inflation factor (vif) indicated no multi-collinearity of explanatory variables (i.e., vif = 1.31). Most of the missing values were participants moving outside the study area, lost forms, and failure to locate the women within 8 weeks postpartum after repeated visits. The missing data, loss of follow-up, and causes were evaluated and not felt to threaten the study's validity. The Cox proportional hazard regression model was employed to identify the association of explanatory variables with NM by consecutive backward elimination. The test of proportional hazard assumption was checked based on the Schoenfeld residuals test (i.e., p -value = 0.24). Adjusted hazard ratio (AHR) with a 95% CI was used to report the results. A $p <$ 0.05 was considered to declare statistical significance.

RESULTS

Among the 2,855 women enrolled in the panel study, 2,240 were currently pregnant, 338 recently postpartum, and 277 were 5–9 weeks postpartum. Finally, 2,481 singleton live birth neonates born to these women were considered in this analysis (**Figure 1**).

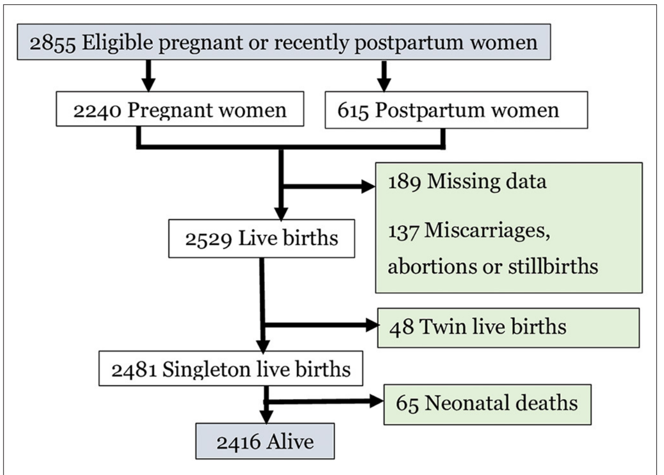

FIGURE 1 | Pregnant or recently postpartum women enrolled, pregnancy outcomes and retained participants for analysis, 2020.

Characteristics of Participants

The mean age of the participants was 27.11 (± 6.11) years. A total of eight hundred twelve (30.41%) women were between the ages of 25 and 29, 2,077 (77.1%) were rural residents, and 1,100 (41.2%) had no formal education. Further, 1,560 (82.70%) participants were multiparas, and 498 (20.06%) were from the middle wealth quintile (**Table 1**).

Neonatal Mortality Rate

The study revealed that the NM rate was 26.84 (95% CI: 19.43, 36.96) per 1,000 live births. During the study period, 2.68% (95% CI: 1.94–3.69%) (n = 65) of the neonates died among 2,481 singleton live births. A total of thirty-two (54%) and 47 (80%) neonatal deaths occurred within the first 2 and 7 days of life, respectively (**Figure 2**).

The log-rank test indicated significant variation of survival pattern to neonatal mortality over the place of residence (X^2 for log-rank test =11.54, $p < 0.01$), wealth quintile (X^2 for log-rank test =11.93, $p = 0.01$), maternal age (X^2 for log-rank test = 14.41, $p < 0.01$), previous pregnancy (X^2 for log-rank test = 5.80, $p =$ 0.01), parity (X^2 for log-rank test = 5.60, $p = 0.01$), and attending at least one ANC visit (X^2 for log-rank test = 4.47, $p = 0.03$; **Table 2**).

Factors Associated With Neonatal Survival

The multivariable analysis indicated that the place of residence, region of dwelling, education level, maternal age, and parity have a significant association with neonatal survival. The neonates born to women of advanced age have two times higher hazard of NM compared to neonates born to women aged 15–19 years (AHR = 2.49, 95% CI: 1.19, 5.21). The hazard of NM was two times higher among neonates born to rural resident women than their urban resident counterparts (AHR = 2.18, 95% CI: 1.05, 4.54). The risk of neonatal mortality was two times higher among neonates born to women living in the Afar region than those in the Tigray region (AHR = 2.42, 95% CI: 1.04, 5.62).

TABLE 1 | Frequency and percentage of study participants' characteristics in Ethiopia 2020 ($n = 2,481$).

Variable	Un-weighted frequency (%)	Weighted frequency (%)
Maternal age		
15–19	250 (9.36)	280 (10.50)
20–24	688 (25.77)	659 (24.69)
25–29	851 (31.87)	812 (30.41)
30–34	483 (18.09)	483 (18.09)
≥35	398 (14.91)	435 (16.31)
Residence		
Urban	1,073 (39.8)	615 (22.9)
Rural	1,621 (60.2)	2,077 (77.1)
Region		
Tigray	420 (16.93)	172 (6.93)
Afar	198 (7.98)	46 (1.83)
Amhara	436 (17.57)	521 (21.01)
Oromia	622 (25.07)	1,099 (44.29)
SNNP	563 (22.69)	551 (22.22)
Addis Ababa	242 (9.75)	92 (3.72)
Wealth quintile		
Lowest	442 (17.82)	516 (20.81)
Lower	373 (15.03)	496 (20.00)
Middle	385 (15.52)	498 (20.06)
Higher	460 (18.54)	490 (19.76)
Highest	821 (33.09)	481 (19.37)
Religion		
Orthodox	1,158 (46.67)	975 (39.29)
Muslim	742 (29.91)	846 (34.09)
Protestant	550 (22.17)	611 (24.61)
Others[a]	31 (1.25)	50 (2.01)
Level of education		
Never attended	946 (38.13)	1,043 (42.06)
Primary	895 (36.07)	982 (39.59)
Secondary	372 (14.99)	279 (11.24)
Technical or vocational	105 (4.23)	79 (3.17)
Higher	163 (6.57)	98 (3.94)
Marital status		
Others[b]	175 (6.55)	135 (5.04)
Married	2,495 (93.45)	2,534 (94.96)
Parity		
Primipara	480 (19.35)	429 (17.30)
Multipara	2,001 (80.65)	1,560 (82.70)
Ever been pregnant		
No	146 (5.47)	127 (4.74)
Yes	2,524 (94.53)	2,542 (95.26)
Antenatal care visit		
No	781 (31.48)	787 (31.72)
Yes	1,700 (68.52)	1,694 (68.28)
Sex of neonate		
Male	1,238 (50.65)	1,261 (51.60)
Female	1,206 (49.35)	1,183 (48.40)

a, Catholic or Traditional or Wakefata; b, widowed or divorced or separated or never married, Weighted, calculated considering weighting factor; Un-weighted, calculated without considering weighting factor.

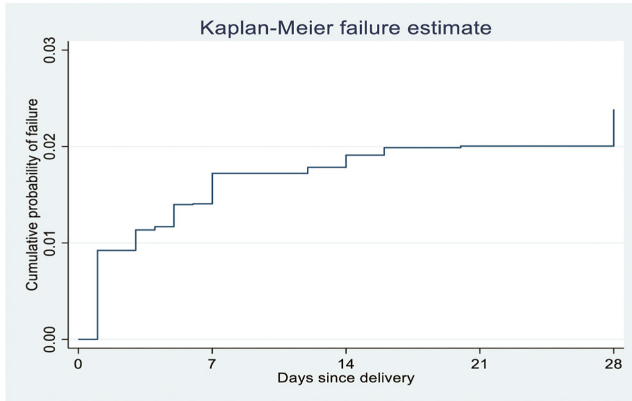

FIGURE 2 | Kaplan-Meier failure estimates of neonatal mortality per day since delivery in Ethiopia, 2020 ($n = 2481$).

TABLE 2 | Result of log-rank test for neonates born to Ethiopian women, October 2019 to September 2020 ($n = 2,481$).

Variable	Log-rank	*P*-value
Residence	11.54	< 0.01
Region	7.35	0.19
Wealth quintile	11.93	0.01
Religion	6.59	0.08
Maternal age	14.41	< 0.01
Educational level	2.95	0.39
Ever been pregnant	5.80	0.01
Parity	5.60	0.01
Antenatal care visit	4.47	0.03
Sex of neonate	2.91	0.08

Similarly, neonates born to primipara mothers had three times higher hazard of NM compared to neonates born to multipara counterparts (AHR = 3.16, 95% CI: 1.52, 6.60).

The hazard of NM among educated women (to the level of technical and vocational training) was 92% lower than those who never attended formal education (AHR = 0.08, 95% CI: 0.01, 0.62; **Table 3**).

DISCUSSION

This study identified the NM rate and factors associated with neonates born to Ethiopian women; the prevalence in Ethiopia was high. Additionally, the factors significantly associated with neonatal mortality were advanced maternal age, rural residence, and primiparity.

The NM rate among neonates born to Ethiopian women was 26.84 per 1,000 live births. Similarly, studies across Ethiopia revealed NM rates of 31.6 (38), 27 (17), and 20.7 (19) per 1,000 live births. The mini DHS 2019 (6), DHS 2016 (5), and analysis based on the DHS (34) also revealed NM rates of 30, 29, and 29 per 1,000 live births, respectively, in Ethiopia.

TABLE 3 | Multivariable Cox proportional hazard regression analysis of predictors of neonatal mortality in Ethiopia, October 2019 to September 2020 ($n = 2,481$).

Variable	Neonatal survival		CHR	AHR
	Censored (%)	Died (%)	(95% CI)	(95% CI)
Residence				
Urban	535 (98.73)	7 (1.27)	1.00	1.00
Rural	1,879 (96.92)	60 (3.08)	2.14 (1.04, 4.39)*	2.18 (1.05, 4.54)*
Region				
Tigray	167 (97.36)	5 (2.64)	1.00	1.00
Afar	43 (95.31)	3 (4.69)	1.61 (0.60, 4.33)	2.42 (1.04, 5.62)*
Amhara	508 (97.47)	13 (2.53)	0.75 (0.28, 2.05)	0.71 (0.26, 1.95)
Oromia	1,067 (97.13)	32 (2.87)	1.04 (0.44, 2.44)	1.06 (0.46, 2.46)
SNNP	537 (97.47)	14 (2.53)	0.81 (0.32, 2.00)	0.74 (0.29, 1.87)
Addis	91 (98.69)	2 (1.31)	0.49 (0.13, 1.85)	0.82 (0.18, 3.59)
Woman's age				
15–19	240 (96.29)	9 (3.71)	1.00	1.00
20–24	586 (98.19)	11 (1.81)	0.51 (0.16, 1.62)	0.93 (0.32, 2.72)
25–29	746 (97.88)	16 (2.12)	0.58 (0.19, 1.77)	1.82 (0.61, 5.38)
30–34	443 (97.28)	12 (2.72)	0.67 (0.20, 2.23)	2.54 (0.68, 4.42)
≥35	400 (95.67)	18 (4.31)	1.23 (0.42, 3.56)	2.49 (1.19, 5.21)*
Level of education				
NAS	1,015 (97.30)	28 (2.70)	0.98 (0.27, 3.51)	0.65 (0.14, 2.89)
Primary	951 (96.85)	30 (3.15)	1.25 (0.35, 4.47)	1.13 (0.28, 4.58)
Secondary	274 (98.19)	5 (1.81)	0.81 (0.19, 3.41)	0.93 (0.18, 4.67)
TeVT	79 (99.81)	2 (1.90)	0.08 (0.01, 0.81)*	0.08 (0.01, 0.62)*
Higher	96 (97.69)	3 (2.31)	1.00	1.00
Wealth quintile				
Lowest	507 (98.21)	9 (1.79)	0.98 (0.40, 2.40)	0.64 (0.23, 1.79)
Lower	474 (95.60)	22 (4.40)	2.32 (0.99, 5.45)	1.50 (0.56, 4.05)
Middle	477 (95.80)	21 (4.20)	2.30 (0.89, 5.39)	1.45 (0.52, 4.00)
Higher	483 (98.60)	7 (1.40)	0.83 (0.30, 2.32)	0.39 (0.15, 0.99)*
Highest	473 (98.38)	8 (1.62)	1.00	1.00
Ever been pregnant				
No	103 (92.80)	8 (7.20)	2.55 (1.15, 5.61)*	2.55 (0.86, 7.52)
Yes	2,311 (97.53)	59 (2.47)	1.00	1.00
Birth events				
Primipara	411 (95.66)	19 (4.34)	2.02 (1.04, 3.89)*	3.16 (1.52, 6.60)*
Multipara	2004 (97.96)	48 (2.04)	1.00	1.00

*CHR, Crude Hazard Ratio; AHR, Adjusted Hazard Ratio; CI, Confidence Interval; NAS, Never Attended School; TeVT, Technical and Vocational Training; Censored – Survived neonates, *Significant at P-value < 0.05 levels; 1.00 – Reference.*

Further, a study in the Somali region of Ethiopia revealed that the NM rate was 57 per 1,000 live births (30). Several factors like prematurity, congenital abnormalities, maternal malnutrition, perinatal asphyxia, and sepsis may be contributary to the high rate (12).

Further, low-health service coverage (i.e., continuum of care), including inaccessible quality maternal and child care, skilled birth attendants, postnatal care, and sociodemographic factors, might contribute to the variations (5). Studies have shown that the NM rate in Ethiopia has been stagnating for a decade. However, the Sustainable Development Goal 3.2 targets the NM rate to reduce the deaths to at least as low as 12 per 1,000 live births by 2030 (39), and the Ethiopian Health Sector Transformation Plan II plans to decrease the NM rate to 21 per 1,000 live births by 2025 (40). Hence, our study alerts policy designers and program implementers that tailored interventions are crucial to reducing the NM to achieve these targets.

The study indicates neonates born to rural residents have an increased hazard of NM compared to their urban counterparts. Similarly, previous studies conducted in Ethiopia (12, 13) found neonates from rural areas have increased chances of death early in life compared to those living in urban areas. Further, women who are uneducated and residing in rural areas are less likely to attend and receive all ANC services available (41), resulting in less or non-use of the continuum of care among rural women, and thus the high risk for NM (9, 12, 42). This leaves significant room for policy development, policies to support neonates born to women in rural areas.

In this study, neonates born to women of advanced age have an increased hazard of NM compared to those aged 15–19 years. Similarly, advanced maternal age has increased the odds of NM in Uganda (15) and Ethiopia (17). A study in Afghanistan also showed advanced maternal age was associated with an increased NM (18). In addition, advanced maternal age is associated with low birth weight (43, 44), preterm (44–47), and other pregnancy complications (47–49), which are associated with NM (12, 50, 51). Further, a study indicated advanced maternal age was associated with unexplained neonatal death (52). This finding highlights the significant role of reducing pregnancy at an advanced maternal age as a strategy to improve neonatal survival.

Neonates born to educated women, who attended vocational and technical training, had a decreased hazard of NM. Similarly, those neonates born to women whose mothers could not read and write had an increased hazard of NM (17). A study in Afghanistan also indicated neonates born to women with higher educational levels had decreased NM (18). This might be due to educated women being more likely to seek healthcare, be autonomous, and be aware of neonatal danger signs. This highlights the fact that female education plays a crucial role to reduce the hazard of NM in Ethiopia.

In this study, neonates born to primipara women have a high hazard of NM compared to their multipara counterparts. A study revealed that neonates born to multipara women had 42% lesser odds of dying compared to their primipara counterparts (32). Similarly, the odds of losing newborns among neonates born to women whose parity was 2–4 and five or more children were lesser than a primipara (28). Furthermore, multiparity reduced the NM by 30% in Ghana and South Africa (53, 54). The odds of delivering a low birth weight newborn were low among multigravida women (55). Multipara women practiced optimal breastfeeding more often than primipara (56, 57), contributing to a lower NM (58). Timely initiation and exclusive breastfeeding may contribute to the prevention of diarrhea-related NM rates (59). The finding highlights the fact that tailored interventions for primipara women are crucial to improving neonatal survival.

Strength and Limitations of the Study

This study utilized nationally representative data and a community-based panel design. Sample weights (household and female) were constructed to minimize selection bias, i.e., compensate for unequal probability selection of clusters and women and non-response bias, thereby, ensuring generalizability. However, recall bias cannot be ruled out since the women have to remember some of the events retrospectively. Misclassification of some stillbirths as early neonatal deaths and loss of follow-up due to failure to locate, movement out of EAs, and death of the women may have occurred in this study. The loss of follow-up was declared after repeated visits to the participants (i.e., maximum of three times), as a result, variables with extensive missing data were not considered during analysis. This panel study did not assess factors such as congenital anomalies, birth trauma, autopsy, interpregnancy interval, and history of neonatal deaths that may predict neonatal mortality. Additionally, further research should assess the relationship between the timeliness, frequency, or contents of ANC visits and NM in the future.

CONCLUSIONS

The NM rate among neonates born to Ethiopian women was unacceptably high. The findings highlight that neonatal survival can be improved through tailored interventions for rural residents, emerging regions, and primipara women, promoting female education and avoiding pregnancy at an advanced maternal age.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the PMA datasets policy does not allow to publish results that communities or individual can be identified or datasets are anonymized before it is made publicly available. It is forbidden to make an effort to identify individual, household, or enumeration areas in the survey, and use the data for marketing and commercial ventures. Access to datasets is granted by PMA Ethiopia upon reviewing the submitted request via www.pmadata.org. Further enquires can be directed to the corresponding author.

ETHICS STATEMENT

Ethical approval was received from Addis Ababa University, College of Health Sciences (AAU/CHS) (Ref: AAUMF 01-008), and the Johns Hopkins University Bloomberg School of Public Health (JHSPH) Institutional Review Board (FWA00000287) by PMA Ethiopia (35). The PMA datasets policy does not allow to publish results that communities or individual can be identified or datasets are anonymized before it is made publicly available. It is forbidden to make an effort to identify individual, household, or enumeration areas in the survey, and use the data for marketing and commercial ventures. Access to datasets is granted by PMA Ethiopia upon reviewing the submitted request. Informed, voluntary consent was obtained from all participants. Thus, all methods were carried out following relevant guidelines and regulations.

AUTHOR CONTRIBUTIONS

KS conceived, designed, analyzed, and prepared a draft of the manuscript. All authors participated in study design, acquisition of data, analysis and interpretation, critical review of the document, and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Serum Vitamin D Insufficiency in Hospitalized Full-Term Neonates at a Tertiary Hospital in Eastern China

Huawei Wang[1†], Yiming Du[1†], Zhixin Wu[1], Haifeng Geng[1], Xueping Zhu[1*] and Xiaoli Zhu[2*]

[1] Department of Neonatology, Children's Hospital of Soochow University, Suzhou, China, [2] Department of Intervention, The First Affiliated Hospital of Soochow University, Suzhou, China

Objective: This study explored the status of serum vitamin D in hospitalized full-term neonates at a tertiary hospital in eastern China.

Methods: A prospective study was conducted among 471 hospitalized full-term neonates at the Children's Hospital of Soochow University between January 1 and June 20, 2020. Perinatal clinical data, serum 25-hydroxyvitamin D (25(OH)D_3), laboratory examinations, serum calcium levels, and immune function were obtained and analyzed. We explored and analyzed the risk factors for vitamin D insufficiency or deficiency, and we also attempted to determine correlations between vitamin D and its influence on immunity.

Results: The mean serum 25(OH)D_3 was 33.65±6.07ng/ml.The prevalence of vitamin D insufficiency was 28.24%,vitamin D sufficiency was 71.76%, there was no vitamin D deficiency. The serum 25-(OH)D_3 in singleton neonate was higher than twins or multiple infants ($t = -10.918$, $P = 0.000$). The serum 25-(OH)D_3 were higher in neonates who born in spring and summer than in winter ($H = 13.443$, $P = 0.001$). The serum 25-(OH)D_3 in appropriate for gestational age (AGA) and large for gestational age (LGA) neonates were higher than small for gestational age (SGA) ($H = 7.686$, $P = 0.021$). The serum 25-(OH)D_3 were higher in neonates whose mothers had no underlying diseases than those with certain immunological and infectious diseases ($F = 12.417$, $P = 0.000$). The serum 25-(OH)D_3 in neonates whose mothers had none or one perinatal complication were higher than those with two or more ($F = 13.299$, $P = 0.000$). The neonates with eosinophils ≤5% or normal platelet counts or serum Ca^{++} ≥0.9 mmol/L have higher serum 25-(OH)D_3. Neonates born in winter were at risk for vitamin D insufficiency, and the incidence of infectious pneumonia, sepsis, cytomegalovirus infection, and hypocalcemia in the vitamin D insufficiency group were higher than sufficiency group ($P < 0.05$). The serum CD3+, CD3+CD4+, and IgA levels in vitamin D sufficiency neonates were significantly higher than those in insufficiency group ($P < 0.05$).

Conclusion: The prevalence of vitamin D insufficiency was 28.24%, and birth in winter was a risk factor for vitamin D insufficiency in hospitalized full-term neonates in Suzhou area. Neonates with infectious pneumonia, sepsis, cytomegalovirus infection, and hypocalcemia exhibited a high risk of vitamin D insufficiency. The serum $CD3^+$, $CD3^+CD4^+$, and IgA levels in neonates with vitamin D insufficiency were lower.

Keywords: Vitamin D, prevalence, insufficiency, deficiency, neonate

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University of Botswana, Botswana

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Prem Fort,
Johns Hopkins All Children's Hospital,
United States
Dipesalema Joel,
University of Botswana, Botswana
Endale Tefera,
University of Botswana, Botswana

***Correspondence:**
Xueping Zhu
zhuxueping4637@hotmail.com
Xiaoli Zhu
zhuxiaoli90@hotmail.com

† These authors have contributed equally to this work

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INTRODUCTION

Vitamin D is key hormone that regulates many essential physiological functions. Vitamin D insufficiency or deficiency is a global health problem which is associated with a variety of diseases, including infectious diseases, metabolic syndrome, and critical illnesses (1). Vitamin D insufficiency or deficiency is very common in populations around the world. It has been reported that most elderly men and women in high-income countries including U.S, Canadian, and European still living in the community are vitamin D deficient (2, 3). Vitamin D deficiency is also common in low-income countries such as Middle East, India, Africa, and South America (4, 5). Children, young and middle-aged adults are at equally high risk for vitamin D deficiency and insufficiency worldwide. The incidence rates and severity of vitamin D insufficiency and deficiency are higher in infants (6–8). A reduction in vitamin D intake and absorption, decreased synthesis, and increased activated 1,25-dihydroxyvitamin D_3 (1,25(OH)2D_3) can lead to severely low levels of vitamin D.

Risk factors for vitamin D deficiency in infant include breast-feeding without vitamin D supplementation and maternal vitamin D deficiency. The infant can remain vitamin D sufficient for several weeks after birth, as long as the mother was vitamin D sufficient. However, most pregnant women are vitamin D deficient or insufficient (9, 10). Lee et al. reported that 76% of mothers and 81% of newborns had a vitamin D deficiency at birth, despite the mothers ingested about 600 IU/d of vitamin D and consumption of two glasses of milk during the period of pregnancy (11).

The vitamin D insufficiency or deficiency is often associated with severe infectious diseases, multiple organ failure, and even mortality (12, 13). Vitamin D signaling imposed a key regulator of immunity in human beings. Vitamin D, also could induce expression of antibacterial proteins which is able to support increased bacterial killing in a variety of cell types (14, 15).

We conducted this study in the Suzhou area of East China to investigate the prevalence of vitamin D insufficiency in hospitalized full-term neonates and to evaluate the factors associated with vitamin D insufficiency. and to explore the relation of vitamin D insufficiency with immunocompromise.

METHODS

Study Design

This study included infants admitted to the neonatal department of the Children's Hospital of Soochow University from January 1 to June 20, 2020. The inclusion criteria were (1) admission age ≤28 days, (2) gestational age ≥37 weeks and <42 weeks, (3) vitamin D and calcium were not supplemented before hospitalization. Exclusion criteria were (1) infants were treated at other hospitals or re-hospitalized, (2) meconium aspiration syndrome (MAS), (3) neonatal acute respiratory distress syndrome (NRDS), (4) complex congenital heart disease and congenital malformation, (5) maternal autoimmune diseases, and (6) discharge against medical advice.

This study was approved by the Ethics Committee of the Children's Hospital of Soochow University (approval number: 2020061). The parents of all infants provided written informed consent.

Diagnostic Criteria and Grouping

Evaluation criteria for vitamin D were adopted according to the Endocrine Society Clinical Practice Guidelines for 25-(OH)D_3 levels: deficiency (<20 ng/mL), insufficiency (20–30 ng/mL), and sufficiency (≥30 ng/mL) (16). We divided the neonates into vitamin D insufficiency and sufficiency groups based on their serum 25-(OH)D_3 levels. Suzhou experiences four seasons: winter (December–February), spring (March–May), summer (June–August), and autumn (September– November).

Clinical Variables

The following data and clinical indices were retrieved from the hospital records: maternal conditions, gestational age, sex, birth weight, age at admission, mode of delivery, perinatal complications (including gestational diabetes, gestational hypertension, gestational anemia, preeclampsia, amniotic fluid contamination, and prenatal infection), and other maternal diseases; laboratory examinations at admission: white blood cell (WBC count [10^9/L]), hemoglobin (Hb [g/L]), eosinophil ratio (%), platelet count ($\times 10^9$/L), C-reactive protein (mg/L), procalcitonin (ng/mL), and serum calcium (mmol/L).

Analytical Biomarker Determination

Blood samples were collected on the day of admission and stored at −80°C. Serum 25(OH)D_3 levels were measured using the Vit k Immune Diagnostic Assay System (Pomade Technology Co. Ltd, Beijing, China).

Statistical Analysis

SPSS 25.0 was used for statistical analyses. Categorical variables were analyzed using either the chi-square test or Fisher's exact test. Normally distributed variables were represented as means ± standard deviations and analyzed using the independent t-test. Non-normally distributed variables were represented as medians ± interquartile ranges [M (P25, P75)], and analyzed using non-parametric tests. Significant factors were identified and multivariate logistic regression analysis was performed to evaluate the risk factors for vitamin D insufficiency. Statistical significance was set at $p < 0.05$.

RESULTS

Patient Enrollment and Characteristics

A total of 471 full-term neonates (male: 290 [59.44%], female: 191 [40.56%], mean gestational age: 39.23 ± 1.06 weeks, median admission age: 5.00 [range: 2.37–13.00] days, mean birth weight: 3389.13 ± 411.16 g, mean admission weight: 3400.78 ± 515.50 g, singleton: 446 [94.69%], twins: 23 [5.31%]) admitted to the Department of Neonatology, Children's Hospital of Soochow University from January 1, 2020 to June 30, 2020, who underwent 25-(OH)D_3 tests, were enrolled in this study.

TABLE 1 | Patient characteristics and clinical outcomes.

Characteristic	Number of cases [n (%)]	$25(OH)D_3$(ng/mL)	t/H/F	*P*-value
Sex				
Male	280(59.44)	33.41 ± 5.73	0.997[a]	0.307
Female	191(40.56)	33.99 ± 6.55		
Delivery mode				
Vaginal delivery	301(63.91)	34.02 ± 6.40	1.782[a]	0.075
Cesarean	170(36.09)	32.98 ± 5.40		
Number of births				
Singleton	446 (94.69)	34.00 ± 6.02	10.918[a]	0.000
Twins or multiple births	23 (5.31)	27.42 ± 2.65		
In vitro fertilization (IVF)				
Yes	12 (2.55)	31.63±4.47	1.166[a]	0.244
No	459 (97.45)	33.70±4.47		
Time of admission (days)				
≤7days	290 (61.57)	33.78 ± 6.29	0.590[a]	0.555
>7days	181(38.43)	33.44 ± 5.71		
Birth season				
Winter*	157 (33.33)	32.29 ± 4.52	13.443[b]	0.001
Spring	228 (48.41)	34.78 ± 6.76		
Summer	86 (18.26)	33.12 ± 6.12		
Birth weight				
SGA*	15 (3.18)	29.85 ± 3.45	7.686[b]	0.021
AGA	434 (92.14)	33.83 ± 6.17		
LGA	22 (4.67)	32.73 ± 4.44		
Feeding type				
Un-feeding	23 (4.88)	33.66 ± 5.69	0.420[c]	0.739
Breastfeeding	224 (47.56)	33.92 ± 6.08		
Formula	62 (13.17)	33.07 ± 5.05		
Mixed Feeding	162 (34.39)	33.48 ± 6.49		

Data are presented as number, number (%), mean (standard deviation).
a, the t-test; b, the Kruskal–Wallis H test; and c, the variance analysis.
**indicates statistically significant differences between the groups.*
SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.

Analysis of Vitamin D Levels and the Influencing Factors

The mean 25-(OH)D_3 level of hospitalized full-term neonates was 33.65 ± 6.07 ng/mL. The prevalence of vitamin D insufficiency was 28.24% (133 cases), and that of vitamin D sufficiency was 71.76% (338 cases); there was no vitamin D deficiency.

The serum 25-(OH)D_3 level in singleton neonates was significantly higher than that in twins or multiple infants ($t = -10.918$, $P = 0.000$). The serum 25-(OH)D3 levels of the neonates born in spring and summer were significantly higher than those born in winter (H = 13.443, $P = 0.001$). The serum 25-(OH)D_3 in appropriate for gestational age and large for gestational age neonates were significantly higher than that in small for gestational age (H = 7.686, $P = 0.021$). There were no statistically significant differences in serum 25-(OH)D_3 levels between the sexes, delivery modes, conception modes, admission age, and postnatal feeding modes among the two groups of neonates ($P > 0.05$) (**Table 1**).

The serum 25-(OH)D_3 levels in neonates whose mothers had no underlying diseases were significantly higher than those born to mothers with immunological diseases (including rheumatoid arthritis, systemic lupus erythematosus, hypothyroidism, and rheumatic heart disease) and infectious diseases (including syphilis, hepatitis B, and prenatal fever) (F = 12.417, $P = 0.000$). Serum 25-(OH)D_3 levels were significantly higher in neonates whose mothers had infectious diseases than in those born to mothers with immunological diseases ($t = -3.136$, $P = 0.004$). The serum 25-(OH)D_3 level in neonates whose mothers had none or one perinatal complication were significantly higher than those with mothers having two or more complications (F = 13.299, $P = 0.000$). There was no statistically significant difference in maternal age ($P > 0.05$) between the groups (**Table 2**).

The serum 25-(OH)D_3 level in neonates with eosinophil ≤5% was significantly higher than that in neonates with eosinophils > 5% (T = 8.556, $P = 0.000$). Serum 25-(OH)D3 levels in neonates with normal platelet counts were significantly higher than in

TABLE 2 | Maternal characteristics.

Characteristic	Number of cases [*n* (%)]	25(OH)D (ng/mL)	t/F	*P*-value
Mother's age, years				
≥35	55 (11.67)	33.58 ± 6.08	−0.608[a]	0.543
<35	416 (88.33)	34.12 ± 6.01		
Underlying disease•				
NO	443 (94.05)	33.98 ± 6.09	12.417[c]	0.000
Immune disease	10 (2.12)	26.80 ± 2.73		
Infectious disease	18 (3.83)	29.30 ± 1.48		
Gestational disease during pregnancy				
NO	327 (69.42)	33.71 ± 5.72	13.299[c]	0.000
1 complication	130 (27.60)	34.33 ± 6.60		
≥2 complications *	14 (2.98)	25.76 ± 2.66		

Data are presented as number, number (%), mean (standard deviation).
a, the t-test; c, the variance analysis.
• The comparison between the two groups was statistically significant.
** indicates statistically significant differences between the groups.*

TABLE 3 | Results of laboratory examinations of neonates.

Characteristic	Cases [*n*, (%)]	$25(OH)D_3$(ng/mL)	*t*	*P*-value
White blood cell count ($\times 10^9$ /L)				
$>20\times10^9$/L or $<4\times10^9$/L	183 (38.85)	33.32 ± 6.20	−0.907	0.365
Normal range	286 (61.15)	33.84 ± 6.01		
Hemoglobin (g/L)				
≥145 g/L	348 (73.89)	33.52 ± 6.24	0.649	0.439
<145 g/L	123 (26.11)	34.01 ± 5.56		
Eosinophil ratio (%)				
>5%	113(23.99)	29.72 ± 3.28	8.556	0.000
≤5%	358(76.01)	34.87 ± 6.12		
Platelets ($\times 10^9$/L)				
$>300\times10^9$/L or $<100\times10^9$/L	225(47.77)	32.95 ± 5.84	−2.412	0.016
$\leq300\times10^9$/L	246(52.23)	34.29 ± 6.23		
C-reactive protein (mg/L)				
≥8 mg/mL	423(89.81)	33.64 ± 6.15	0.061	0.951
<8 mg/mL	48(10.19)	33.70 ± 5.38		
Procalcitonin (ng/mL)				
≥0.5 ng/mL	107(22.71)	34.27 ± 6.27	1.217	0.224
<0.5 ng/mL	364(77.29)	33.46 ± 6.01		
Serum calcium ion (mmol/L)				
≥0.9 mmol/L	405(85.99)	34.23 ± 6.18	−7.589	0.000
<0.9 mmol/L	66(14.01)	30.04 ± 3.73		

Data are presented as number, number (%), mean (standard deviation).

TABLE 4 | Multivariate logistic regression analysis predicting the risk vitamin D insufficiency in full-term neonates.

Variable	β	SE	Wald	*P*	OR	95% CI
Birth in winter	1.138	0.258	19.458	40.000	0.320	0.193–0.531

those with abnormal platelet counts ($t = -2.412$, $P = 0.016$). The serum 25-(OH)D_3 in neonates with serum Ca^{++} ≥0.9 mmol/L was significantly higher than that in neonates with serum Ca^{++} <0.9 mmol/L ($t = -7.589$, $P = 0.000$). There were no statistically

TABLE 5 | Comparison of vitamin D sufficient and insufficient groups.

Characteristics	Vitamin D insufficiency *n* (%)	Vitamin D sufficiency *n* (%)	χ^2	*P*-value
Infectious diseases				
Infectious pneumonia	44 (33.08)	76 (22.48)	5.646	0.017
Enteritis	12 (9.02)	28 (8.28)	0.067	0.796
Urinary infection	18 (13.53)	35 (10.35)	0.966	0.326
Sepsis	7 (5.26)	5 (1.47)	4.862	0.044
Bacterial meningitis	2 (1.52)	5 (1.50)	0.000	0.984
CMV infection	7 (5.26)	6 (1.77)	4.393	0.036
Non-infectious diseases				
Pathological jaundice	40 (30.07)	80 (23.67)	2.063	0.151
Hypocalcemia	28 (21.05)	38 (11.24)	7.623	0.006
Hemolytic disease	9 (6.76)	32 (9.46)	0.876	0.349
Neonatal vomiting	6 (4.51)	17 (5.02)	0.055	0.814
Neonatal asphyxia	3 (2.25)	7 (2.07)	0.016	0.900
Hydronephrosis	5 (3.75)	13 (3.84)	0.002	0.965
ASD	35 (26.31)	90 (26.62)	0.005	0.945
VSD	6 (4.51)	14 (4.14)	0.032	0.858
PDA	3 (2.25)	12 (3.55)	0.184	0.471
Subarachnoid hemorrhage	20 (15.03)	47 (13.91)	0.099	0.770

Data are presented as number, number (%).
CMV, cytomegalovirus; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus.

significant differences ($P > 0.05$) in vitamin D levels regarding WBC count, hemoglobin, C-reactive protein and procalcitonin at admission (**Table 3**).

Multifactorial Analysis of Vitamin D Insufficiency

Multivariate logistic regression analysis based on the statistically significant factors associated with vitamin D insufficiency, revealed that being born in winter was a risk factor for vitamin D insufficiency in full-term neonates (**Table 4**).

Comparison of Diseases Between Vitamin D Groups

The incidence rates of infectious pneumonia, sepsis, cytomegalovirus infection, and hypocalcemia were higher in the vitamin D insufficiency group than those in the sufficiency group ($P < 0.05$).

The incidence rates of enteritis, urinary tract infection, bacterial meningitis, pathological jaundice, hemolytic disease, vomiting, neonatal asphyxia, hydronephrosis, atrial septal defect, ventricular septal defect, and patent ductus arteriosus were not significantly different between the two groups ($P > 0.05$) (**Table 5**).

Correlation of Serum Vitamin D With Immunological Indicators

Among the 471 full-term neonates, 380 exhibited immunological indicators. The serum CD3+, CD3+CD4+, and IgA levels in the vitamin D sufficient group were significantly higher than those in the insufficiency group ($P < 0.05$). However, there were no significant differences in serum CD3+CD8+, CD4+/CD8+, CD3-CD19+, CD3-CD16+CD56+, complement C3, complement C4, IgM, and IgG between the two groups ($P > 0.05$) (**Table 6**).

DISCUSSION

This study indicates that vitamin D insufficiency is associated with being born in winter. Moreover, we observed that the prevalence of vitamin D insufficiency in neonates with infectious pneumonia, sepsis, cytomegalovirus infection, and hypocalcemia was higher and the serum CD3+, CD3+, CD4+, and IgA levels were lower in neonates with vitamin D insufficiency.

In our prospective study, we found that the prevalence of vitamin D insufficiency was 28.24%, the vitamin D sufficiency was 71.76%, and there was no vitamin D deficiency in our hospital. A similar study in Boston, northeastern USA, revealed that the prevalence of serum vitamin D insufficiency (25-(OH)D3, 20–30ng/mL) in neonates with gestational age ≥37 weeks was 24.7% (17). The incidence of vitamin D insufficiency in preterm neonates was not included in this study. There are regional and lactation differences regarding neonatal serum vitamin D and associated with vitamin D deficiency during pregnancy (18). Suzhou city is located near the ocean, latitude 30°47′-32°2′ (mid-latitude region), with warm weather and adequate sunlight. The region has a flourishing economy and commerce. During pregnancy, women consciously ensure that they receive sufficient vitamin D by supplementation, which is why we found no vitamin D deficiency in hospitalized full-term neonates. Also we thought the pregnant mother in our region get enough Vitamin D supplement, further, we need to

TABLE 6 | Correlation of serum vitamin D with immunological indicators.

Characteristics	Vitamin D insufficiency (n = 96)	Vitamin D sufficiency (n = 284)	t/U	P-value
$CD3^+$ [%, ($\bar{x} \pm s$)]	78.97 ± 6.70	82.75 ± 6.99	−3.646[a]	0.000
$CD3^+CD4^+$ [%, ($\bar{x} \pm s$)]	57.61 ± 6.75	59.90 ± 7.52	−2.242[a]	0.026
$CD3^+CD8^+$ [%, ($\bar{x} \pm s$)]	21.14 ± 5.27	22.10 ± 6.23	−1.353[a]	0.177
$CD4^+/CD8^+$ [%, ($\bar{x} \pm s$)]	2.93 ± 1.03	2.99 ± 1.21	−0.474[a]	0.636
$CD3^-CD19^+$ [%, ($\bar{x} \pm s$)]	9.46 ± 5.09	8.99 ± 4.42	−1.288[a]	0.199
$CD3^-CD16^+CD56^+$ [%, ($\bar{x} \pm s$)]	9.56 ± 5.57	8.97 ± 5.75	−1.70[a]	0.142
complement C3 [g/L, ($\bar{x} \pm s$)]	0.63 ± 0.15	0.66 ± 0.16	−1.466[a]	0.144
complement C4 [g/L, ($\bar{x} \pm s$)]	0.15 ± 0.05	0.15 ± 0.06	−0.876[a]	0.381
IgA [g/L, ($\bar{x} \pm s$)]	0.04 ± 0.02	0.05 ± 0.03	−3.608[a]	0.000
IgM [g/L, M(P_{25}, P_{75})]	0.15(0.09, 0.21)	0.13(0.07, 0.23)	−0.218[d]	0.828
IgG [g/L, ($\bar{x} \pm s$)]	8.49 ± 2.02	8.47 ± 1.87	−0.511[a]	0.586

Data are presented as mean (standard deviation), or median (interquartile range).
a, t-test; b, Kruskal–Wallis H-test.

continue exploring the serum of maternal Vitamin D influence on the infants.

Our findings revealed that being born in winter was an independent risk factor for vitamin D insufficiency in full-term neonates. We all know that the major source of vitamin D for children and adults is exposure to natural sunlight (19). This widely accepted association between vitamin D insufficiency status and the season of birth was reported by Mosayebi et al. (20). They found that the majority of neonates with vitamin D insufficiency were born on cold days during the winter, and the vitamin D status was closely related to the season of birth. The correlation between vitamin D status and the season of birth has also been reported by Khuri-Bulos et al. (21) who showed that most neonates with low levels of vitamin D were born during the winter months. However, other studies did not identify a specific relationship between the season of birth and serum vitamin D levels in neonates (22). It appears that exposure to sunlight is not a critical factor for serum vitamin D status. The synthesis of vitamin D is affected by various factors such as latitude, season, air pollution, and clothing. Vitamin D is primarily synthesized by exposure of the skin to direct sunlight. Receiving breast milk, which chronically contains low levels of vitamin D and certain customs of ancient cultures that reduce direct sun exposure would contribute to the deficiency or insufficiency of vitamin D in neonates (23). Consequently, some research has shown that vitamin D was not being produced, not only in regions at latitudes of 45° or higher (such as North America and Europe), but also during special periods, including winter, which may last 6 months of the year or longer (24). Moreover, some studies revealed other factors that may affect the vitamin D status in neonates, such as mothers with restricted sun exposure inducing maternal vitamin D deficiency, preterm babies, and small for gestational age (25).

Low serum vitamin D levels in neonates are associated with rickets, bronchopulmonary dysplasia (BPD), respiratory tract infections, and other diseases (26–28). A previous study revealed that neonates with vitamin D deficiency or insufficiency are at greater risk of developing serious infection and sepsis, and lower serum vitamin D levels in pregnant mothers are closely linked with increased risk of sepsis in neonates (29). A study also showed that 25 hydroxy vitamin D level of children in the NRDS group was significantly lower than that of the non-NRDS group (SMD $= -0.51$, 95%CI: -0.63 to -0.39, $p \leq 0.05$). Suggests that vitamin D deficiency is very likely to be a high-risk factor of NRDS, and reasonable vitamin D supplementation during pregnancy and after birth is of great significance (30). In other related fields, a study in Taipei revealed that the prevalence of vitamin D deficiency was 59%, and only 10% of critically ill patients had a vitamin D level >30 ng/mL. They also found that most critically ill patients had a median vitamin D level <20 ng/mL during their stay at the intensive care units (31).

In our study, the serum $CD3^+$, $CD3^+CD4^+$, and IgA levels in neonates with vitamin D insufficiency were lower. Vitamin D has other functions as well, including modulating activated B and T lymphocytes, insulin, and thyroid-stimulating hormone secretion (32). Vitamin D potentially influences human immunity, including the induction of antimicrobial peptides (AMPs) and suppression of T-cell proliferation. Infants with rickets are at risk of developing diseases unrelated to calcium homeostasis, including immune disorders, and a study showed that immune production of 25-(OH)D is regulated by factors that are not linked to calcium homeostasis. Local synthesis of 25-(OH)D and its downstream signaling are integral components of innate immune responses to microbes (33). Another study reported that locally produced 25-(OH)D activated the transcription of certain signaling pathways and genes related to innate immunity. In laboratory studies, the gene encoding CD14, the co-receptor of the pattern recognition receptor toll-like receptor-4, is strongly induced by 25-(OH)D (34). Clinical and epidemiological studies have reported that the immune protection induced by vitamin D could protect the body from some viruses, including hepatitis viruses, human immunodeficiency virus, and viral respiratory pathogens (35).

In our analysis, several limitations were noted. We did not identify whether suboptimal maternal vitamin D status directly contributed to the neonates. Further, our study did not include data on prenatal vitamin D supplementation and maternal 25(OH)D levels and therefore, did not facilitate better risk prediction regarding suboptimal vitamin D status.

CONCLUSIONS

Vitamin D is key hormone that plays an important role in human health. Vitamin D insufficiency or deficiency is a global health problem which is associated with a variety of diseases. Results from this study suggest the prevalence of vitamin D insufficiency in neonates is high, and birth in winter was a risk factor for vitamin D insufficiency in hospitalized full-term neonates. Neonates with infectious pneumonia, sepsis, cytomegalovirus infection, and hypocalcemia exhibited a high risk of vitamin D insufficiency. The serum $CD3^{+}$, $CD3^{+}CD4^{+}$, and IgA levels in neonates with vitamin D insufficiency were lower. We believe that suppling and remain the neonates Vitamin D sufficiency will improve initiatives for optimizing neonate care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Children's Hospital of Soochow University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HW and YD participated in the study design and manuscript writing. ZW and HG collected clinical data collection and conducted data analysis. XuZ and XiZ supervised the design and execution of the study, performed the final data analysis, and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Development of a Nomogram for Clinical Risk Prediction of Preterm Neonate Death in Ethiopia

Habtamu Shimels Hailemeskel[1]* *and Sofonyas Abebaw Tiruneh*[2]

[1] Department of Pediatrics and Neonatal Nursing, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia,
[2] Department of Public Health, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia

Introduction: In 2020, over 6,500 newborn deaths occured every day, resulting in 2.4 million children dying in their 1st month of life. Ethiopia is one of the countries that will need to step up their efforts and expedite progress to meet the 2030 sustainable development goal. Developing prediction models to forecast the mortality of preterm neonates could be valuable in low-resource settings with limited amenities, such as Ethiopia. Therefore, the study aims to develop a nomogram for clinical risk prediction of preterm neonate death in Ethiopia in 2021.

Methods: A prospective follow-up study design was employed. The data were used to analyze using R-programming version 4.0.3 software. The least absolute shrinkage and selection operator (LASSO) regression is used for variable selection to be retained in the multivariable model. The model discrimination probability was checked using the ROC (AUROC) curve area. The model's clinical and public health impact was assessed using decision curve analysis (DCA). A nomogram graphical presentation created an individualized prediction of preterm neonate risk of mortality.

Results: The area under the receiver operating curve (AUROC) discerning power for five sets of prognostic determinants (gestational age, respiratory distress syndrome, multiple neonates, low birth weight, and kangaroo mother care) is 92.7% (95% CI: 89.9–95.4%). This prediction model was particular (specificity = 95%) in predicting preterm death, with a true positive rate (sensitivity) of 77%. The best cut point value for predicting a high or low risk of preterm death (Youden index) was 0.3 (30%). Positive and negative predictive values at the Youden index threshold value were 85.4 percent and 93.3 percent, respectively.

Conclusion: This risk prediction model provides a straightforward nomogram tool for predicting the death of preterm newborns. Following the preterm neonates critically based on the model has the highest cost-benefit ratio.

Keywords: preterm, death, prediction, nomogram, Ethiopia

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Susan Coffin, University of Pennsylvania, United States

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Xiaoliang Huang, Affiliated Tumor Hospital of Guangxi Medical University, China
Krysten North, Harvard Medical School, United States

****Correspondence:***
Habtamu Shimels Hailemeskel
habtamushimels21@gmail.com

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INTRODUCTION

Preterm birth is defined by the World Health Organization as any birth occurring before 37 weeks of pregnancy or within 259 days of a woman's last regular menstrual period (LMP) (1). An estimated 15 million babies are born each year prematurely (2).

Evidence from different studies showed that birth weight, gestational age, marital status, required resuscitation after delivery, no antenatal care, plurality of pregnancy, sex of neonate, respiratory distress syndrome (RDS), hypothermia, not initiating exclusive breastfeeding, mode of delivery, non-cephalic presentation, fifth minute APGAR score < 7, did not receive kangaroo mother care (KMC) were risk factors in preterm mortality (3–9).

In 2020, over 6,500 newborn deaths occured every day, resulting in 2.4 million children dying in their 1st month of life (10, 11). Neonates mainly die due to preterm birth. Complications from preterm birth are the leading cause of death in children under five. Preterm complications account for 35 percent of total newborn fatalities in 2017, according to WHO and the Maternal and Child Epidemiology Estimation Group estimates (12). Each year, almost one million neonates and children under five die due to preterm birth problems (13, 14). Compared to Europeans, preterm newborns had 12 times higher risk of death in Africa. Preterm birth is the second most significant cause of under-five death in Sub-Saharan Africa, accounting for 12.1 percent, while preterm or low birth weight accounts for more than half of newborn mortality in East Africa (15). Preterm birth and associated complications account for more than one-fifth of newborn death in Ethiopia (15–20).

Predictive models are used to help clinicians determine if a clinical disease exists (diagnostic models) or whether an event will occur within the time frame (prognostic models) to aid in decision-making (21). Risk assessment and outcome prediction are critical tools (22). Predictions can be utilized in the prognostic context to construct therapeutic decisions based on the risk of developing a given result or event within a specific time frame (23). Predictions made by clinicians without using prediction tools are highly unreliable in the care of premature infants.

Continuous positive airway pressure (CPAP), surfactant administration for newborns with RDS, and phototherapy for jaundiced neonates are among the WHO recommendations from 2015 to increase the chances of survival and health outcomes for preterm infants. However, most of the above-mentioned preterm care facilities, such as radiant warmers, CPAP, surfactant, mechanical ventilators, and phototherapy, are sparse or non-existent in most of Ethiopia's public hospitals. As a result, developing predicted probability models to forecast the mortality of preterm neonates could be beneficial, especially in low-resource settings with limited resources. Predictive models developed in developed countries might not be suitable for developing countries because they vary with the use of Biomarkers, sophisticated facilities, and devices that are not readily accessible due to resource or practical limitations in low-resource settings.

A predictive model allows real-time preterm neonates risk stratification, which guides primary attention to care for the good health outcome of the neonates. There is no study on the risk prediction of preterm neonatal mortality in Ethiopia. Identifying prognostic predictors of preterm mortality in the setting would be vital to decrease deaths of preterm mortality and meet sustainable development goal (SDG) targets on time. According to the Lancet report, if all nations achieved the SDG newborn mortality target by 2030, more than 5 million deaths may be averted over the next 10 years (24). Two-thirds of Sub-Saharan African countries, on the other hand, are on the verge of missing the SDG newborn death target. More than half of these nations must triple their current annual rate of reduction (ARR) for newborn mortality to accomplish the SDG target on time, and another 14 countries must at least double their current ARR. Ethiopia is one of the countries that will need to step up its efforts and accelerate progress to meet the SDG target if it is to meet it by 2030 (10, 11, 14). Therefore, this study tries to develop a nomogram for clinical risk prediction of preterm neonate death in Ethiopia, 2021.

MATERIALS AND METHODS

Study Design, Area, and Period

A prospective institutional-based observational study design was employed in South Gondar zone public hospital, Northwest Ethiopia. Among eight public hospitals, this study was done in Addis- Zemen primary hospital, Wegeda primary hospital, Nefas Mewcha primary hospital, and Debretabor General Hospital. The study was conducted from December 2020 to May 2021.

Eligibility Identification

All preterm neonates delivered and admitted in South Gondar Zone Public Hospitals were a source population. Preterm neonates who were delivered in the labor ward and admitted to NICU within 72 h of life were included in the study. Pregnant women without reliable last menstrual period or pregnant women without an early ultrasound report (first tri - minister), incomplete prenatal, delivery, and neonatal chart, and preterm neonates without parents were excluded during the data collection period.

Sample Size Determination and Sampling Procedure

Since there is no prior prediction study for preterm neonates' death in a similar setting to calculate the sample size, as the rule of thumb, ten events/preterm neonate death/per covariates were considered. Thirteen covariates were recruited in the final model from a total of 36 prognostic maternal and neonatal determinants based on literature or clinical experience. From a total of 456 neonates prospectively followed, there were 132 preterm neonate deaths that occurred.

Preterm neonates delivered from December 1, 2020 to May 30, 2021, delivered and admitted in a neonatal intensive care unit (NICU) in South Gondar zone public hospitals, were included. Eligible participants came up in the labor ward and admitted neonatal intensive care unit with consecutive sampling techniques. Proportional allocation based on the monthly average number of preterm delivered and admitted has been determined for each public hospital. We followed 204 preterm neonates at Debre Tabor Hospital, 76 preterm neonates at MekaneEyesus Hospital, 112 preterm neonates at Wegeda Hospital, and 28 preterm neonates at AdisZemen Hospital for 6 months during the data collection period.

Measurement and Data Collection Procedure

We have used a reliable last menstrual period or an early ultrasound (first trimester) to determine gestational age. Data were collected based on an adapted interview-administered questionnaire and reviewing medical records. The questionnaire was adapted by reviewing different pieces of literature, including maternal socio-demographic, maternal medical, obstetric, prenatal, and neonatal variables, including age of the mother, the residence of the mother (urban, rural), marital status (union/non-union), pre-pregnancy body mass index, mother occupation, mother education, gestational age (late, moderate, very, extremely very preterm), parity, current pregnancy complications [preeclampsia/eclampsia/pregnancy-induced hypertension, preterm premature rupture of membrane, antepartum hemorrhage (APH), cord prolapse, and Rh factor], birth interval, antenatal care (ANC) follow-up, the plurality of the child (single, multiple), pregnancy intension (wanted/unwanted), mode of delivery, presentation, magnesium given for this pregnancy, antenatal steroids given or not, sex of the neonate, birth weight, age of the neonate, any resuscitation during delivery, sepsis, perinatal asphyxia (PNA), feeding status, APGAR score, kangaroo mother care (KMC) given or not, type of preterm (spontaneous or induced), respiratory distress syndrome (RDS), hypothermia, jaundice, congenital anomaly, and hypoglycemia.

The data were collected by 12 BSc neonatal nurses and four assistant lecturers in nursing supervisors. Trained data collectors interviewed mothers who were at 28 to less than 37 weeks (36 + 6 days) gestation at the labor ward and were abstracted pregnancy, delivery, and infant data from the chart and followed during a 24-h period until discharge, transfer, death, or 42 postmenstrual ages after birth, and their outcome was recorded.

Infant death between birth and 42 postmenstrual ages was declared dead. Neonates beyond 42 postmenstrual ages, referred to, and left with medical advice, were declared alive.

Neonatal morbidity was immediate neonatal complications, including (APGAR score, RDS, hyperbilirubinemia, and sepsis of preterm infants within 42 PMAs after birth (7). Sepsis is defined as clinical sign symptoms with risk factors in lab tests (microscopic) greater than two hematologic criteria (25). "Neonatal respiratory distress was diagnosed with the presence of one or more symptoms of tachypnea, intercostal muscle retraction, grunting, nasal flaring, and cyanosis" (26). Birth asphyxia is defined as "the failure to initiate and sustain breathing at birth."

Data Quality Control

Questionnaires were pretested with a 5% sample size at Mekane Eyesus primary hospital. The training was given for data collectors and supervisors for 1 day before and 1 day after the pretest regarding the study's objective, data collection tool, and ways of data collection and checking the completeness of the data collection tool.

Data Management and Analysis

Epi-Data version 4.6 software was used to enter the data. R-programming version 4.0.5 was used to analyze the data. In the beginning, variable selection in the multivariable model was made using least absolute shrinkage and selection operator (LASSO) regression. Two-sided *P*-values of less than 0.05 were considered statistically significant.

Model calibration was assessed by plotting declines of the predicted probability of preterm death in each decline and fitting a smooth line. The model discrimination probability was checked by using the area under ROC (AUROC) curve. "givitiR" R-packages were used to check the calibration plot. Bi-normal smoothing bootstrapping technique was used to validate AUROC internally. After bootstrapping, the model's predictive performance was considered the performance that can be expected when the model is applied to future similar populations. Decision curve analysis (DCA) was used to evaluate the model's clinical and public health impact.

The Youden index value, which classified high or low risk, was used to predict the likelihood of preterm death. Sensitivity, specificity, and the positive and negative predictive values were computed. The probability of preterm death for each neonate was predicted using the linear predictor of estimated risk of death, which is: P (Risk score for each patient) = risk score X prognostic determinant + ... + N (risk score) X N (prognostic determinant). Additionally, a nomogram graphical presentation was prepared to construct an easily clinically applicable individualized prediction of preterm neonate risk of death.

Ethical Considerations

The study participants were informed about the purpose, risk, benefits, and confidentiality of the study, and informed and voluntarily signed written consent has been obtained during the interview previously. Ethical approval was obtained from Debre Tabor University, College of Health Sciences, and the Institutional Review Board (IRB).

RESULTS

Maternal Socio-Demographic Characteristics

A total of 456 preterm neonates were involved in this study. The median age of the respondents was 26 years. Most of the respondents (95.6%) were married, followed by single status (3.5%). Thirty-eight percent of the respondents were unable to read and write. Regarding the occupation of the respondents, 364 (79.8%) of them were housewives, and 68 (14.9%) of them were employees. Three hundred (65.8%) of the respondents were rural residents (**Table 1**).

Maternal Obstetric-Related Characteristics

Of the total respondents, one hundred seventy-two (37.7%) were Para-one. Most of the mothers (97.4%) have ANC follow-up during this pregnancy. Four hundred sixteen (93.7%) have four times and above ANC follow-up among those with ANC follow-up. About the delivery route, the majority (91.2%) of mothers had vaginal route delivery. Seventy-six (16.2%) of the mothers encountered complications during this pregnancy. APH

TABLE 1 | Maternal socio-demographic characteristics in south Gondar zone public hospitals, northwest Ethiopia, 2021.

Variable	Category	Frequency	Percent
Marital status	Single	16	3.5
	Married	436	95.6
	Divorce/windowed	4	0.9
Educational status	Unable to read and write	177	38.8
	Read and write	17	3.7
	Primary(1–8)	166	36.4
	Secondary(9–12)	40	8.8
	College and above	56	12.3
Occupation	Housewife	364	79.8
	Employed	68	14.9
	Merchant	12	2.6
	Student	12	2.6
Residence	Urban	156	34.2
	Rural	300	65.8
Pre-pregnancy BMI	Less than 18.5	88	19.3
	18.5–24	220	48.2
	Greater than 24	148	32.5

TABLE 2 | Maternal obstetric-related characteristics in south Gondar zone public hospitals, northwest Ethiopia, 2021.

Variables	Category	Frequency	Percent
Parity	One	172	37.7
	Greater than one	284	62.3
ANC	Yes	444	97.4
	No	12	2.6
No of ANC	Two	4	0.9
	Three	24	5.4
	Four and above	416	93.7
Route of delivery	Vaginal route	416	91.2
	Cesarean section	40	8.8
The plurality of the neonate	Singleton	336	73.7
	Multiple	120	26.3
Presentation	Cephalic	440	96.5
	con –Cephalic	16	3.5
Complication during this Pregnancy	Yes	76	16.7
	No	380	83.3
Type of complication	RH negative	4	5.2
	APH	24	31.6
	PIH	16	21.1
	Prolonged/Obstructed	8	10.4
	Urinary tract infection	4	5.2
	Cord Prolapse	4	5.2
	Premature rapture of membrane(PROM)	12	15.6
	Maternal fever	4	5.2
Antibiotics given in this Admission for the index pregnancy	Yes	24	5.3
	No	432	94.7
Pregnancy intention	Wanted	452	99.1
	Unwanted	4	0.9

was the most common one 24 (31.6%) among those who had complications during this pregnancy. The median afterbirth interval of the respondents was 36 months for those gravid two and above (**Table 2**).

Neonatal-Related Characteristics

One hundred eighty-four (40.4%) of neonates were with gestational age between 32 and 34 weeks. Two hundred forty (52.6%) of the neonates were male (**Table 3**).

Immediate Morbidity of Preterm Neonates

One-fourth of the neonates had RDS. The majority (89.9%) of preterm neonates were hypothermic during admission. Thirty-six percent of preterm neonates were diagnosed with sepsis. Forty-four (9.6%) preterm neonates had PNA. Seven percent (27) of the preterm neonates had hypoglycemia (**Table 4**).

A Predictive Model for Preterm Neonates Death

The maternal socio-demographic, obstetric, and neonatal-related prognostic determinants were considered to predict preterm mortality. In the final model, the plurality of the neonate (multiple) has no RDS, gestational age of less than 32 weeks, low birth weight, and KMC were the remaining significant predictors of preterm mortality (**Table 5**).

After the multivariable logistic model, a total of five prognostic determinants were left for the prediction of preterm mortality, and the relative contribution of each prognostic determinant to the probability of preterm mortality was calculated by dividing each beta coefficient by the lowest beta coefficient and rounding to the nearest integer (score chart rule formula) (**Table 6**).

Therefore, the probability of preterm mortality among preterm neonates using the **linear** prediction formula was:

Linear predictor of the model (l p) = −1.54 + 2.66 * gestational age less than 32 weeks + 0.77 *multiple pregnancy-4.4; *has no RDS, + 2.1; *has not gotten KMC, + 1.52; *low birth weight.

Model Discrimination Probability and Calibration Plot

The area under the receiver operating characteristics curve (AUROC) had a discrimination power of 92.7% (95% CI: 89.9–95.4) (**Figure 1A**). The final prediction model was good calibrated (p-value = 0.519) (**Figure 1B**). The prediction model was particular (specificity = 95%) in its ability to predict preterm death, with a true positive rate (sensitivity) of 77%. This prediction had a low false-positive rate of 4% among the actual death of the preterm neonates. The model prediction accuracy was 90% (**Supplementary File 1**). The prediction model was internally validated using 2,000 bootstrap replicates.

Model Cost-Benefit Analysis (Decision Curve Analysis)

The cost-benefit analysis of the prediction model was compared between no follow-up for all the preterm neonates, followed by

TABLE 3 | Neonatal-related characteristics among preterm neonates in south Gondar zone public hospitals, northwest Ethiopia, 2021.

Variables	Category	Frequency	Percent
Gestational age	Less than 32 weeks	76	16.7
	32–34 weeks	196	43.0
	Greater than 34 Weeks	184	40.4
Any resuscitation at delivery	Yes	36	7.9
	No	420	92.1
Sex	Male	240	52.6
	Female	216	47.4
Type of preterm	Spontaneous	448	98.2
	Induced	8	1.8
Type of feeding	Breast milk	252	55.3
	Express breastfeeding by nasogastric tube	108	23.7
	Formula milk	4	0.9
	Nothing per mouth	92	20.2
Gestational age for weight	Appropriate for gestational age	440	96.5
	Small for gestational age	16	3.5
KMC	Yes	110	24.1
	No	346	75.9

TABLE 4 | Immediate morbidity among preterm neonates in south Gondar zone public hospitals, North West Ethiopia, 2021.

Morbidities	Category	Frequency	Percent
RDS	Yes	116	25.4
	No	340	74.6
Hypothermia	Yes	410	89.9
	No	46	10.1
Sepsis	Yes	164	36.0
	No	292	64.0
PNA	Yes	44	9.6
	No	412	90.4
Jaundice	Yes	56	12.3
	No	400	87.7
Congenital anomaly	Yes	8	1.7
	No	448	98.3
Hypoglycemia	Yes	36	7.9
	No	420	92.1

all the preterm neonates, and critically follow selectively based on these predictors. For example, if we critically follow all preterm neonates at a threshold risk of death probability of 30%, we will find 30% prevalence of preterm death. Whereas, if we follow the preterm neonates based on the prediction model, the preterm neonates need critical follow-up at the risk of preterm death threshold of more than 80%. Therefore, following the preterm neonates selected based on the model has the highest cost-benefit ratio (**Figure 2**).

Nomogram for Prediction of Preterm Death

To construct an easily clinically applicable individualized prediction of preterm neonate risk of death was prepared in nomogram graphical presentation (**Figure 3**). The best threshold (Youden index) cut point value was 0.3 (30%) to predict a high or low risk of preterm death (**Figure 1A**). The maximum sensitivity and specificity of the Youden index cut point value were 83.3 and 94.4%, respectively (**Figure 1A**). The positive predictive and negative predictive values at the Youden index threshold value were 85.4 and 93.3%, respectively. The linear predictor of five parameters is estimated in the probability of preterm death in the nomogram to predict the preterm neonate death. For example, if a preterm neonate was born with multiple births, low birth weight, and the preterm neonate was not under KMC, the predicted probability of preterm death is calculated as follows. The total point for the three predictors was the sum of each predictor point, which was 1.8 + 3.5 + 4.8 = **10.1.** Therefore, the probability of preterm death with the corresponding total points in the nomogram was 0.2 (20%), indicating a low risk of preterm death. Whereas a preterm neonate had RDS and low birth weight, the total points were 10 + 4.8 = 14.8. Thus, the probability of preterm death, approximately 0.68 (68%), is declared a high risk of preterm death (**Figure 3**).

DISCUSSION

In our study, a combination of five sets of prognostic determinants (gestational age, RDS, multiple neonates, low birth weight, and KMC) results in the discernment power of area under the receiver operating curve (AUROC), 92.7% (95% CI: 89.9–95.4%). Having an e in the model's AUROC of 0.93 indicates that it is 93 percent accurate incapable of distinguishing between preterm neonates who died and those who survived. The higher the AUC indicates, the better the model predicts dead preterm neonates' classes as death and alive preterm neonates' classes as alive The area under the ROC curve (AUC) results was reflected excellent for AUC values between 0.9 and 1 (28, 29). Because it had an outstanding measure of separability of dying from alive preterm neonates, it is of paramount importance if the physician employs this tool to anticipate preterm neonates' mortality. Following the preterm neonates selectively based on the model's tool has the highest cost-benefit ratio by considering the false-positive rate.

Clinicians can determine the likelihood of preterm neonate risk of mortality by adding each value of the prognostic factors that the neonate possesses from the nomogram. This study's nomogram graphical display offers a clinically useful customized prediction of preterm neonate death risk. The prognostic predictor of five factors was assessed in the probability of preterm death in the nomogram to predict preterm neonate death.

In this study, the maximum sensitivity and specificity of the Youden index cut point value were 83.3 and 94.4%, respectively. It means that this tool has an 83% probability of correctly identifying all those who do, indeed, have died from among preterm neonates who have died and the probability of avoiding neonates who have not died when they have. Similarly, this model has a 94% probability of correctly identifying; from among preterm neonates who do not die, all those who do, indeed, have not died and not categorizing some neonates

TABLE 5 | Multivariate binary logistic regression results among preterm neonates in south Gondar zone public hospitals, North West Ethiopia, 2021.

Variables	Category	Death		COR (95% CI)	AOR (95% CI)
		Yes	No		
Marital status	Union	120	316	1	1
	Not union	12	8	4 (1.58, 9.90)	1.13 (0.22, 5.91)
The plurality of the neonate	Singleton	76	260	1	
	Multiple	56	64	2.99 (1.93, 4.65)	**2.6 (1.19, 5.58)**
Presentation	Cephalic	124	316	1	
	Non-cephalic	8	8	2.55 (0.94, 6.94)	4.4 (0.63, 31.34)
Neonate Sex	Male	92	148	1	
	Female	40	176	0.37 (0.24, 0.56)	1.3 (0.59, 2.69)
RDS	Yes	96	20	1	**1**
	No	36	304	0.02 (0.014, 0.05)	**0.02 (0.01,0.04)**
Antenatal corticosteroid given	Yes	6	28	1	1
	No	126	296	1.99 (0.80, 4.92)	0.40 (0.11, 1.52)
GA	Less than 32 weeks	52	24	1	**16.3 (6.04, 44.14)**
	32–36 + 6 weeks	80	300	0.12 (0.07,0.21)	**1**
Hypothermia	Yes	126	284	2.96 (1.22, 7.15)	1.8 (0.53, 6.15)
	No	6	40	1	**1**
PNA	Yes	28	16	1	1
	No	104	308	0.19 (0.10,0.37)	0.52 (0.17, 1.62)
Sepsis	Yes	68	96	1	1
	No	64	228	0.4 (0.26, 0.60)	0.60 (0.26, 1.37)
Birth weight	≥2500	20	117	1	**1**
	Less than 2500	112	207	3.17 (1.87, 5.36)	**4.1 (1.70, 9.78)**
KMC given	Yes	9	101	1	**1**
	No	123	223	6.19 (3.02, 12.67)	**10.1 (3.36, 30.7)**
Route of delivery	Vaginal	292	124	1	**1**
	Cesarean	32	8	0.589 (0.26,1.733)	0.5. (0.21,1.2)

Bold = significant.

TABLE 6 | Prognostic determinants in south Gondar zone public hospitals, northwest Ethiopia, 2021.

Prognostic determinants	AOR (95% CI)	Regression coefficient	Contribution to risk score
The plurality of the neonate (multiple)	2.6 (1.19, 5.58)*	0.77	1
Has no RDS	0.02 (0.01, 0.04)***	−4.4	6
Gestational age less than 32 weeks	16.3 (6.04, 44.14)***	2.66	4
Low birth weight	4.1 (1.70, 9.78)***	1.52	2
Kangaroo mother care is not given	10.1 (3.36, 30.7)***	2.1	3
Constant−**1.54**			

*N.B.: Significant codes: ***< 0.001, * <0.05.*

as died when, in fact, they do not die (30). These findings suggest that this prediction had a low false-positive rate among actual preterm neonatal deaths, indicating an essential role in predicting preterm birth.

At the Youden index threshold value, the positive and negative predictive values were 85.4 and 93.3%, respectively. This indicates that this tool has an 85 percent chance of correctly identifying all newborns that have died from among preterm neonates who may or may not have died and not categorizing some neonates as dead while they are alive. Furthermore, this tool has a 93 percent chance of correctly identifying all neonates who do not die among preterm neonates who may or may not die while correctly categorizing some neonates as alive when they are not. It accurately predicted that the neonate perished and, if true, projected that the neonate was alive. It has good predicted the neonate died and if was died and predicted the neonate was alive if was alive. As a result, it can accurately predict preterm mortality.

In this study, RDS is one prognostic determinant for preterm mortality. It is similar to different studies on neonatal mortality prediction (31, 32). The possible justification might be the lack of surfactant in premature newborns, which

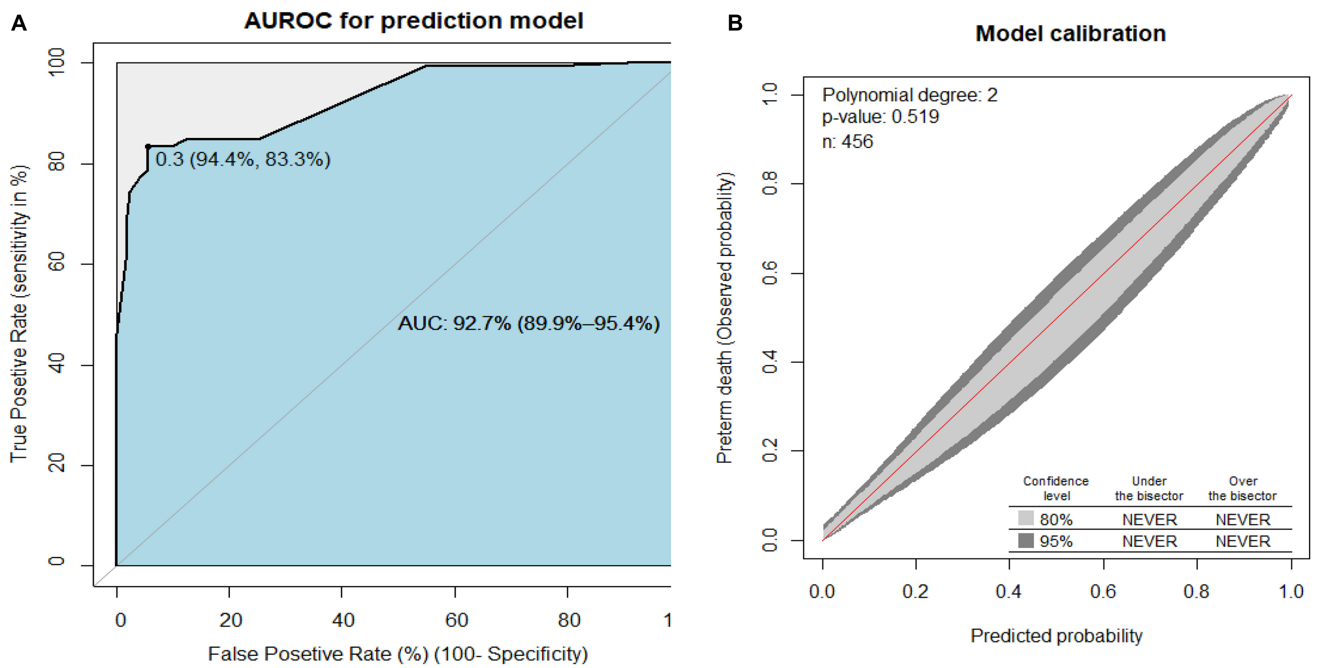

FIGURE 1 | (A) Area under the receiver operating characteristics curve (AUROC) for the reduced prediction model and **(B)** the prediction model calibration plot to predict preterm birth neonates.

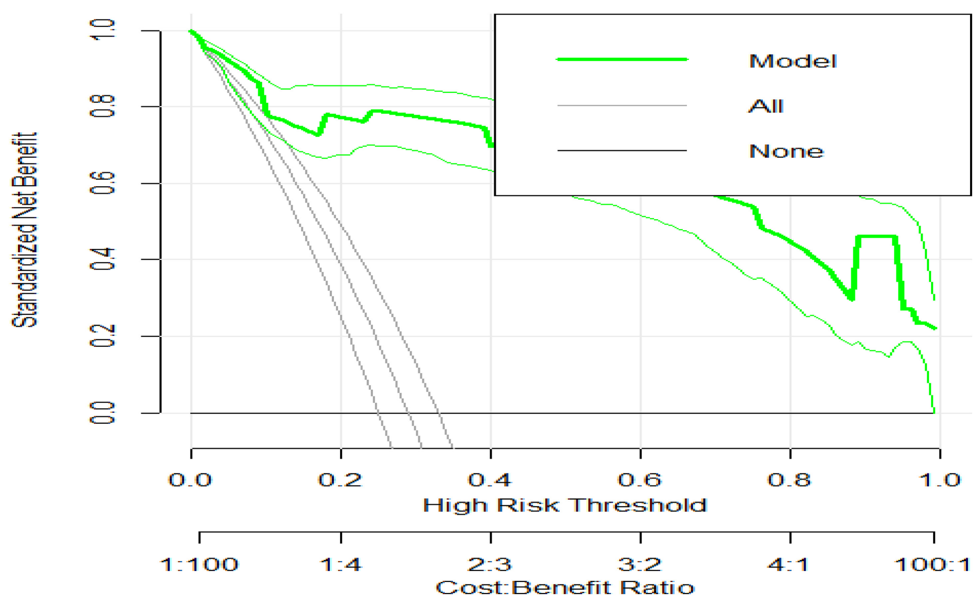

FIGURE 2 | Decision curve analysis for prediction of preterm neonates' death.

raises the surface tension inside the small airways and alveoli, limiting the immature lung's compliance and causing hypoxemia and lactic acidosis. In addition to a lack of surfactant, the preterm infant's immature lung has lower compliance, decreased fluid clearance, and immature vascular development, all of which predispose the lung to damage and inflammation, complicating the normal development of alveoli and pulmonary vasculature (33). This may further complicate and increase neonatal mortality.

Gestational age less than 32 weeks was another prognostic determinant for preterm mortality. It is consistent with different studies on the prediction of neonatal mortality (31, 32). The possible justification might be that better physiological and immunological maturity occurs as gestational age increases.

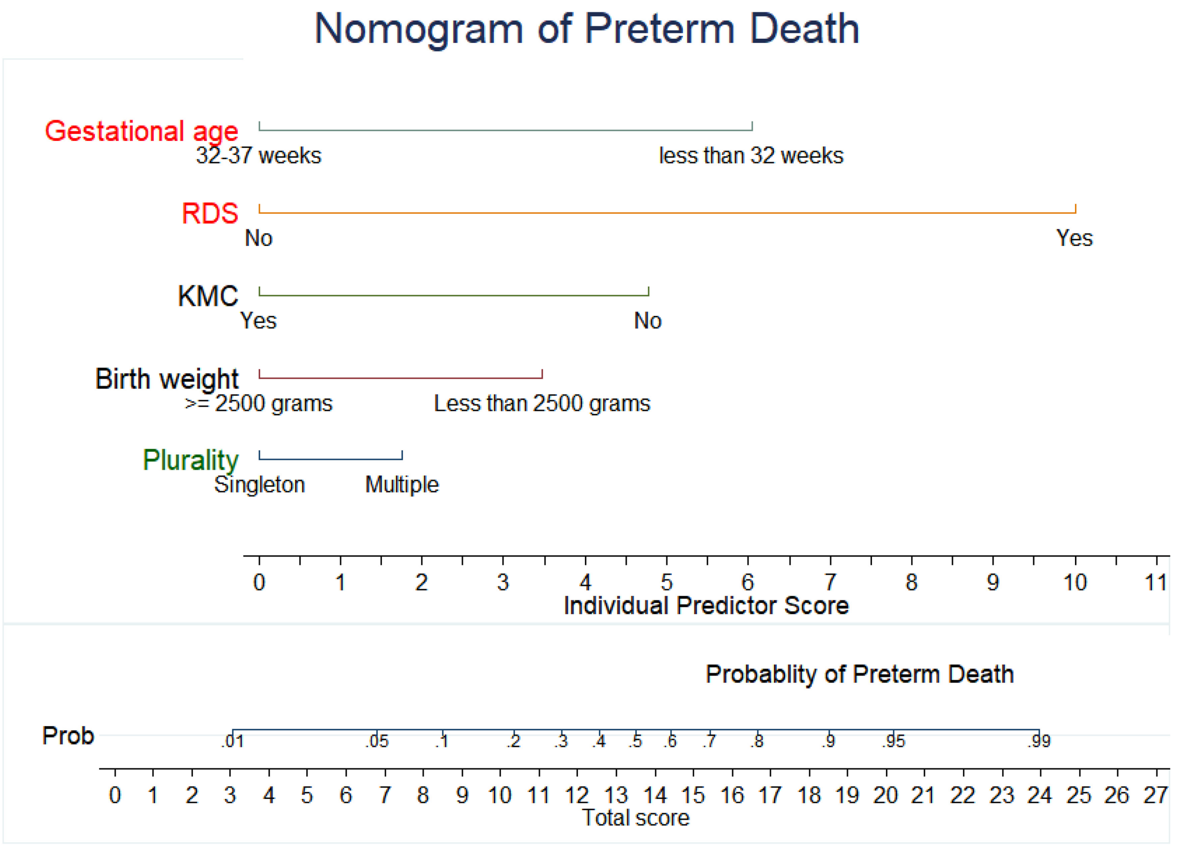

FIGURE 3 | Nomogram of a prognostic model to estimate the probability of preterm death.

Multiple neonates are one prognostic determinant for preterm mortality. It is similar to a study done in Ohio that revealed that twin pregnancy was predicted risk of adverse pregnancy outcomes, including neonatal death (34). It might be due to twins being more likely LBW because of restricted growth and increased rates of obstetric complications, such as premature separation of the placenta and had perinatal neonatal complications. Multiple births are high-risk pregnancy and birth (35, 36).

Low birth weight is one prognostic determinant for preterm mortality. This might be lower birth weight (16) prone the neonate to metabolic disorders and other complications that increase the risk of death. It is consistent with different studies on premature infants (33, 37) and among both term and preterm neonates (38, 39).

Kangaroo Mother Care is one prognostic determinant for preterm mortality. One reason is that KMC prevents hypothermia, which causes neonatal mortality (27, 32). KMC offers many more benefits besides thermal protection, notably a successful initiation and maintenance of lactation and preventing apnea of prematurity. So it averted the death of preterm neonates. KMC markedly reduces neonatal mortality among preterm babies and significantly decreases severe morbidity, especially from infection (37, 38).

CONCLUSION

In our study, a combination of five sets of prognostic determinants (gestational age, RDS, multiple neonates, low birth weight, and KMC) was estimated in the probability of preterm death in the nomogram. This nomogram can be used to graphically predict the risk of death among preterm neonates. In settings with similar demographics, the risk prediction tool can assist clinicians and health care providers to predict preterm neonates' death and target interventions. Following the preterm neonates based on the selectively using the model has the highest cost-benefit ratio.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Debre Tabor University, College of

Health Sciences, and Institutional Review Board (IRB). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HH was involved in conceptualization, methodology, data cleaning, data analysis, interpretation, drafting, reviewing, and revising of the manuscript. ST was involved in methodology, data cleaning, data analysis, interpretation, drafting, reviewing, and revising of the manuscript. Both authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

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Appraising Neonatal Morbidity and Mortality in a Developing Country Categorized by Gestational Age Grouping and Implications for Targeted Interventions

Olugbenga Ayodeji Mokuolu[1,2†], Omotayo Oluwakemi Adesiyun[1,2†], Olayinka Rasheed Ibrahim[1], Habibat Dirisu Suberu[1], Selimat Ibrahim[3], Surajudeen Oyeleke Bello[1], Moboni Mokikan[4], Temitope Olorunshola Obasa[1,2] and Mohammed Baba Abdulkadir[1,2]*

[1] Neonatal Intensive Care Unit, Department of Pediatrics, University of Ilorin Teaching Hospital, Ilorin, Nigeria, [2] Department of Pediatrics and Child Health, College of Health Sciences, University of Ilorin, Ilorin, Nigeria, [3] Centre for Malaria and Other Tropical Diseases Care, University of Ilorin Teaching Hospital, Ilorin, Nigeria, [4] Department of Biostatistics and Epidemiology, East Tennessee State University, Johnson City, TN, United States

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Andrew Steenhoff, Children's Hospital of Philadelphia, United States

Reviewed by:
Nisha Keshary Bhatta, B. P. Koirala Institute of Health Sciences, Nepal
Rajkumar Meshram, Government Medical College, Nagpur, India

***Correspondence:**
Olugbenga Ayodeji Mokuolu
mokuolu@unilorin.edu.ng

†These authors have contributed equally to this work and share first authorship

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Introduction: Despite the relatively higher neonatal morbidity and mortality in developing countries, there are limited data on the detailed analysis of the burden in Nigeria. With a database of over 14,000 admissions, this study presents a compelling picture of the current trends disaggregated by their gestational age groups. It provides unique opportunities for better-targeted interventions for further reducing newborn mortality in line with SDG 3, Target 3.2.

Methods: This prospective observational study involved newborn babies admitted to the Neonatal Intensive Care Unit of the University of Ilorin Teaching Hospital, Kwara State, Nigeria, between January 2007 and December 2018. The outcome was the neonatal mortality rates. The exposure variables included birth weight, gestational age (preterm versus term), and clinical diagnosis. Frequencies were generated on tables and charts, and the trends or associations were determined.

Results: Of the 14,760 neonates admitted, 9,030 (61.2%) were term babies, 4,847 (32.8%) were preterm babies, and in 792 (5%) of the admissions, the gestational ages could not be determined. Males constituted a higher proportion with 55.9%, and the total number of deaths in the study period was 14.7%. The mortality ratio was highest among babies with a birth weight of less than 1,000 g (38.0%) and gestational age of less than 28 weeks (65.5%). The trend analysis showed that the mortality rate decreased from 17.8 to 13% over the 12 years, p-value < 0.0001. For term babies, mortality decreased by 45%, from 15.7% in 2007 to 8.7% in 2018, while the decline in mortality for preterm babies was 28.4%, from 25.7% in 2007 to 18.4% in 2018. For both categories, p-values were < 0.001. Regarding morbidity in term babies, asphyxia occurred in (1:3), jaundice (1:5), sepsis (1:6), and respiratory disorders (1:6) of admissions. For mortality, asphyxia occurred in (1:2), sepsis (1:5), jaundice (1:8), and respiratory disorders (1:10) of deaths. The leading causes of morbidity among preterm babies were asphyxia (1:4), sepsis (1:5), respiratory disorders (1:9), and jaundice (1.10). For mortality, their contributions were asphyxia (≈1:2); sepsis (1:5); respiratory disorders (1:9), and jaundice (1:10).

Conclusion: There was a marked improvement in neonatal mortality trends. However, severe perinatal asphyxia, sepsis, hyperbilirubinemia, and respiratory disorders were the leading conditions contributing to 75% of the morbidities and mortalities. Measures to further accelerate the reduction in neonatal morbidity and mortality are discussed.

Keywords: neonatal mortality, low-middle-income country, preterm, term babies, sustainable development goals

INTRODUCTION

Globally, substantial progress was made toward the achievement of now rested fourth Millennium Development Goal (MDG) with a reduction of almost half in the number of under-five deaths from 1990 to 2013 (1, 2). During the same period, infant mortality reduced from 63 to 34 per thousand live births, while neonatal mortality rate decreased from 33 to 20 per thousand live births (3). In Nigeria, the neonatal mortality rate also decreased from 52 to 37 per thousand live births (4). To achieve these milestones, the federal government scaled up interventions in 2007 by rolling out the Integrated Maternal, Newborn, and Child Health (IMNCH) strategy, implemented by most states in Nigeria (5–8). The government also introduced the Midwives Service Scheme (MSS) a few years later, focusing on safe delivery, especially in rural areas (9). Furthermore, Nigeria's partnerships with United States Agency for International Development (USAID), Saving Newborn Lives/Save the Children-US, the Partnership for Reviving Routine Immunization in Northern Nigeria (PRRINN), -WHO, and UNICEF have all contributed to the progress made (5, 10).

Although there is progress in neonatal indices, a more significant burden still occurs in low-and middle-income countries than in high-income countries. In 2017, the neonatal mortality rate was highest in Sub-Saharan Africa (27 deaths per 1,000 live births), about nine times higher than the average of three deaths per 1,000 live births in high-income countries (11). Most neonatal deaths in low-income countries occur in preterm and low birth weight babies. A multi-countries global network study showed the highest mortality rates were for infants born weighing < 1,500 grams, with rates of approximately 700/1,000 births for India and Pakistan. Similarly, the study also showed a higher death rate among those with the lowest gestational age (12).

Appraising neonatal mortality causes in Nigeria, or probably in many developing countries, has been somewhat challenging. Large-scale studies were done using verbal autopsy techniques at community levels. The country's demographic health survey indicated a slow decline in the neonatal mortality rate from 42 in 1990 to 39 per 1,000 live births in 2018 (4, 13). The studies mentioned above have many limitations with the current data gathering methods. This may explain, for instance, the complete absence of neonatal jaundice and thermoregulatory problems as a cause of mortality in the newborn (13). Furthermore, the contributions of preterm babies and their specific morbidities are often not reflected. Hence a holistic picture of neonatal mortality would require an appraisal of community and hospital-based data stratified by the gestational categories. A few reports have attempted to describe the hospital-based neonatal mortality and morbidity trends. However, they have often included relatively small numbers. They tend to have significant limitations in the disease categorizations, especially among preterm babies (14–18).

The adoption of the Sustainable Development Goals (SDGs) by the United Nations General Assembly appears to be an opportunity to reset and recalibrate several health indices as new targets are rolled out against the target date of 2030. For instance, SDG 3 has as one of its components that;

> *"by 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births"*(19).

The intentions expressed in this goal emphasize the need to end preventable deaths. A hospital-based report showed perinatal rates of 81/1,000 and neonatal mortality rates of 31/1,000 live births (20). Due to differences in access to health and available infrastructures, there are significant variabilities in the causes of morbidity/mortality from place to place. Hence, the need to determine region-specific mortality. We, therefore, hypothesized that the trends of neonatal mortality rate differ over the study period due to the impact of the pragmatic approach. This study presents 12-year prospectively gathered data on neonatal morbidity and mortality, as seen at the University of Ilorin Teaching Hospital, Nigeria. With a database of over 14,000 admissions, with over 4,500 preterm babies, this study presents a compelling picture of a developing country's current trends among term and preterm babies. It identifies unique opportunities for better-targeted interventions to recalibrate further efforts to reduce newborn mortality in line with SDG 3.

METHODOLOGY

Study Site

The study was carried out at the neonatal intensive care unit (NICU) of the University of Ilorin Teaching Hospital, Nigeria. Ilorin in Kwara State, Nigeria. The University of Ilorin Teaching Hospital is a 600-bed facility referral hospital. However, due to the weaknesses in the referral systems, it also offers significant degrees of primary and secondary level care services. Hence, a hospital-based study from the facility also significantly reflects the community distribution of newborn morbidity and mortality. The NICU provides level II-a care to newborn babies from the hospital's labor and delivery unit and outborn babies from other parts of Kwara and the adjoining states (21). The facility has an annual admission rate of 1,300–1,500 newborns (22).

Study Design

This was a prospective observational study. A special register was created *a priori* to capture all admissions data using the Microsoft Excel software package. The data capture form was printed out and bound for ease of entry by the doctors on the ward. This register was distinct from the regular hospital register of admissions that the nurses often complete. The data capture register was designed to enhance the documentation of important variables like the hierarchy of diagnosis, gestational age, duration of admission, and necessary treatments. All newborn babies admitted at the University of Ilorin Teaching Hospital (UITH) over 12 years (January 2007 to December 2018) had their data entered into this register by unit Junior Residents. The Consultants supervised the data entry and ensured the validity of the information entered. The outcomes were updated at discharge or deaths of the babies.

Study Participants

The study included all the neonates (inborn and out-born babies) at the UITH during the study period.

Neonatal Care Practices

Each baby admitted to the Unit received standard care based on its protocols for managing their clinical conditions, including relevant blood culture, complete blood counts, serum bilirubin, and radiological investigations. The gestational ages were assessed using the last normal menstrual period and the new Ballard score within 24 h of admission (23). Unfortunately, the gestational ages could not be documented in some cases, especially when the last menstrual period (LMP) or ultrasound (USS) dates were unavailable. The babies were older than 72 h at presentation. Besides, Lubchenco et al.'s (24) chart was used to classify the babies. Those that presented for admission after 72 h had their gestational age group identified as unclassified. The Lubchenco chart applies to Nigerian newborn babies (25).

Neonatal care is largely anticipatory and mainly addresses the newborn's basic needs. These needs are;

The need to be pink—This comprises measures taken to ensure adequate cardiopulmonary transition and maintenance through a baby's stay on the ward. Oxygen delivery is through the appropriate technologies of oxygen concentrators and piped oxygen from the hospital oxygen plant (26). There is limited capacity to support respiration using bubble C-PAP, a BiPAP machine, or IPPV.

The need to be warm—We introduced some innovative measures to create an appropriate mix of modern and relevant technologies to provide a suitable ambiance for the babies; these include digitally recycled incubators and locally fabricated radiant heaters (27). These are used concurrently with standard radiant warmers and modern incubators to provide a neutral thermal environment.

The need to be sweet refers to the provision of adequate calories. Babies with initial respiratory difficulties or other identified contraindications to oral feeds are commenced on glucose infusion after birth. Otherwise, there is an early introduction of trophic feeds using the mother's breast milk administered as gavage feeding or direct breastfeeding, depending on the babies' conditions. There was daily monitoring of the babies' weights until there was consistency in weight gain, and after that, monitored weekly.

The need to be clean—Maintaining asepsis is addressed by observing strict handwashing between patient contacts, restriction of access to the unit, and maintenance of aseptic procedures.

Other care: These are provided according to the specific problems identified in the babies, such as managing hyperbilirubinemia, administration of blood transfusion, or corrective surgical procedures for some congenital or acute surgical conditions.

Upgrade and changes in neonatal care practices: The unit witnessed improved technology and human capacity during the study period. Firstly, the old incubators were refurbished in 2005 with enhanced performance (27). In 2009, the unit also moved to a purposely built ward, and Vamed Engineering Limited supplied and maintained a new set of incubators. In 2011, improvised bulb CPAP was introduced. From 2013 to 2015, the neonatal resuscitation program was held regularly for the NICU and labor ward staff. In addition, a resident was posted to labor to provide support for newborns delivered in the hospital.

Follow-up care: Upon discharge, babies are seen regularly at either of the two clinics. One is the outpatient services operated by the neonatal unit, while the other is the growth and development clinic in the pediatric outpatient department. The length of follow-up is determined by the nature and severity of the admitting condition.

Definitions of Terms and Criteria Used for Diagnosis

Term babies: Babies born at completed 37 to 42 weeks of gestational age (28).

Preterm babies: Babies born at less than 37 completed weeks (28).

Post-term: Babies born after the completed 37 weeks (28).

Perinatal asphyxia: This was based on the history of failure to cry at birth with evidence of neurological involvement at admission (29).

Sepsis was defined as the presence of signs and symptoms of infections with evidence of systemic inflammatory response on laboratory evaluations (30).

Hyperbilirubinemia: was defined as elevated serum bilirubin based on age and gestational age (31).

Bilirubin encephalopathy: Presence of elevated serum bilirubin with evidence of neurological involvement (31).

Data Analysis

Admission and hospital data were entered into the specially designed data capture program on a Microsoft Excel spreadsheet in the unit. The data were analyzed weekly at the unit level and presented at the monthly departmental clinical meetings. The data was further analyzed annually. The captured data were exported to SPSS version 20 to generate frequency tables, charts, and the chi-square test for trends.

RESULTS

General Characteristics

A total number of fourteen thousand, seven hundred and sixty neonates (newborn babies within the first 28 days of life) were admitted to the NICU during the study period. Males numbered eight thousand, two hundred and fifty-four (55.9%) while females numbered six thousand five hundred and six (44.1%), giving a male to female ratio of 1.3:1. The total number of deaths recorded within the period was two thousand, one hundred and seventy-seven, with a percentage mortality of 14.7%. See **Table 1**. Overall, there was a significant downward slope in the relative mortality (**Figure 1**); Chi-square for the trend gave a p-value < 0.0001.

Of the total admissions of 14,760, there were 9,030 (61.1%) term babies, 4,938 (33.5%) preterm babies, and in 792 (5.4%) of the admissions, the gestational ages could not be determined. These were primarily babies admitted after 72 h with parents not having relevant antenatal information for gestational age assessment. Comparing the contributions of term and preterm babies to admission and mortalities among babies with known

TABLE 1 | Summary of newborn admissions and outcomes (2007–2018).

Parameters	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Total admission	1,208	1,390	1,560	1,476	1,213	1,451	1,476	1,034	985	843	942	1,182	14,760
Males	670	811	869	764	693	817	817	603	551	471	527	661	8,254
Females	538	579	691	712	520	634	659	431	434	372	415	521	6,506
Deaths	215	259	267	204	166	204	207	150	137	88	122	158	2,177
%Mortality*	17.8	18.6	17.1	13.8	13.7	13.9	14.0	14.5	14.1	10.4	13.0	13.4	14.7

Chi-square for linear trend (χ^2) = 53.0964, df = 1, p = <0.0001.

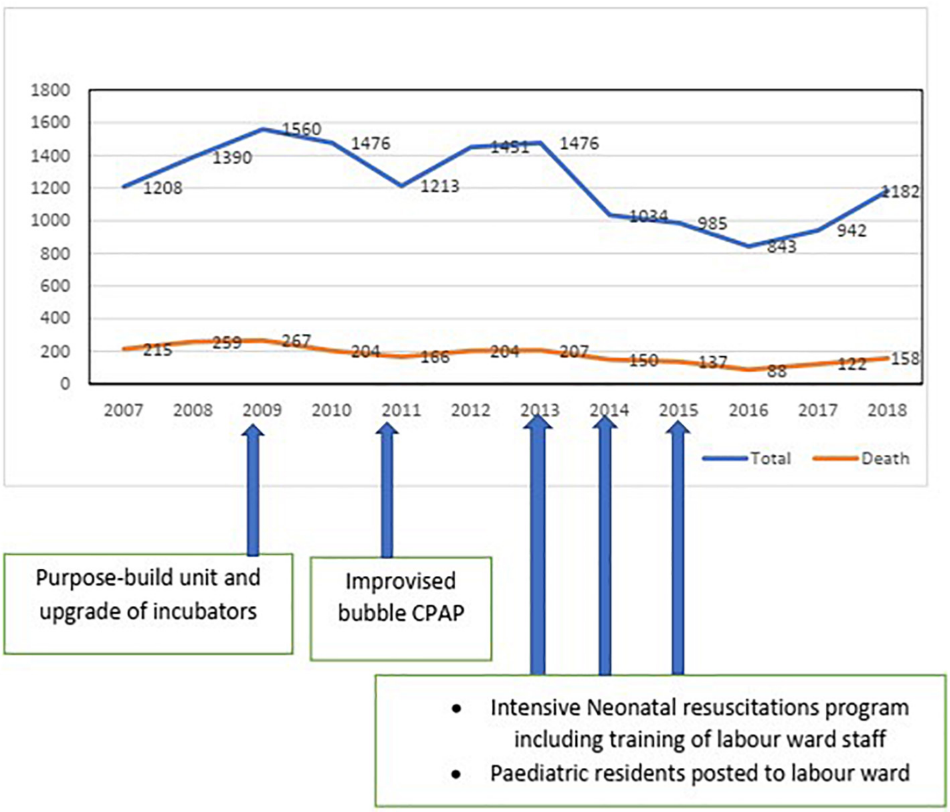

FIGURE 1 | Admission and mortality trends with timing of interventions during the study period.

gestational ages, the results indicate that term babies accounted for 61.1% of admissions and 49.2% of mortalities, while preterm contributed 32.8% of admissions and 45.2% of mortality ($\chi^2 = 179.6$; $p < 0.00001$).

Trends in Mortality Among Term Babies

Term babies (37–42 completed weeks of gestation) were nine thousand and thirty, accounting for 61.1% of the total number of admissions. One thousand and fifty-seven died, giving a case fatality of 11.7% for term babies. There was a downward trend in the annual proportion of mortality among term babies from 15.7% in 2007 to 8.7% in 2018, with chi-square for trend (χ^2) = (2) = 56.1673 df = 1, $p < 0.0001$. Further sub-analysis of the deaths indicated that for the period 2007–2009, the proportion of deaths for term babies was 12.8% (/2912) while deaths for the period 2013–2018 was 9.4% (412/4409); $X^2 = 555.79$, $p = 0.00001$, OR = 1.33 (95% CI: 1.13–1.59)]. However, the mortality rate between 2010–2012 (11.0%; 273/2766) vs 2013–2018 (9.4%; 412/4409) were comparable, 2 = 0.543, $p = 0.461$ (see **Table 2**).

Trends in Mortality Among Preterm Admissions

Preterm babies (gestational age less than 37 weeks) were four thousand nine hundred and thirty-eight, representing 33.5% of the total admissions within the period. A total number of nine hundred and ninety-eight preterm babies died over the 12 years of the study, representing 20.2% of their admissions. See **Table 3**. There was a significant decline in the proportion of preterm mortality relative to their admissions from 25.7% in 2007 to 17.3% in 2017. chi-square for trend (χ2) = 11.1672, df = 1, $p = 0.0008$. Further analysis showed that proportion of death declined from 2007–2009 (20.0%; 347/1737) compared with periods of 2010 to 2012 (15.7%; 234/1255), and 2013 to 2018 (18.2%; 417/2710) with 2 values of 9.861, $p = 0.002$ and 15.670, $p = 0.001$, respectively. However, the proportion of death between 2010–2012 and 2013 to 2018 was comparable (2 = 0.078, $p = 0.799$).

Causes of Morbidity and Mortality Among Term Babies

The leading causes of morbidity among term babies included perinatal asphyxia (PA) (35%), hyperbilirubinemia (18%), neonatal sepsis (16%), respiratory distress (13%), congenital malformation (7%), macrosomia (2%) and others (9%) as shown in **Figure 2**. The leading causes of death included perinatal asphyxia (50%), neonatal sepsis (18%), bilirubin encephalopathy (11%), respiratory distress (9%), congenital malformation (7%), hematological problems (1%), and others (4%) as shown in **Figure 3**.

Causes of Morbidity and Mortality Among Preterm Babies

The causes of morbidity among preterm babies included perinatal asphyxia (24%), neonatal sepsis (19%), respiratory distress (17%), hyperbilirubinemia (10%), anemia of prematurity (4%), intraventricular hemorrhage (2%), others (3%) and 19% of the total preterm babies were admitted for routine care (**Figure 4**). The causes of death included perinatal asphyxia (36%), neonatal sepsis (24%), respiratory distress (16%), bilirubin encephalopathy (7%), intraventricular hemorrhage (6%), congenital malformation (4%) and others (7%) as shown in **Figure 5**.

Distribution of Mortality by Birth Weight

The distribution of mortality based on birth weight showed that the highest percentage of mortality (38%) was among newborns who weighed less than 1,000 g, while the lowest rate of mortality (8%) was among babies who weighed ≥ 4,000 g. More details of percentage mortality based on birth weight are shown in **Figure 6**.

Distribution of Mortality by Gestational Age

The highest percentage of mortality (63.6%) was among babies with gestational age < 28 weeks, while the least percentage of mortality (9.6%) was among those with gestational age 34–36 weeks. The other details are shown in **Figure 7**.

TABLE 2 | Admissions and mortality trends in Term babies 2007–2018.

Admission	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Term	752	822	966	867	756	870	885	650	604	521	589	748	9,030
Deaths	118	126	128	78	84	111	94	72	62	48	71	65	1,057
% Mortality*	15.7	15.3	13.3	9.0	11.1	12.8	10.6	11.1	10.2	9.2	12.1	8.7	11.7

Chi-square for linear trend (χ^2) = 56.1673 df = 1 p < 0.0001.

TABLE 3 | Preterm babies' admissions and mortality 2007–2018.

Admission	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Preterm	452	465	473	481	360	414	459	349	376	322	353	434	4,938
Death	116	116	115	100	63	71	79	70	68	60	60	80	998
% Mortality*	25.7	24.9	24.3	20.8	17.5	17.1	17.2	20.9	18.1	18.6	17.3	20.0	20.2

Chi-square for linear trend (χ^2) = 11.1672, df = 1, p = 0.0008.

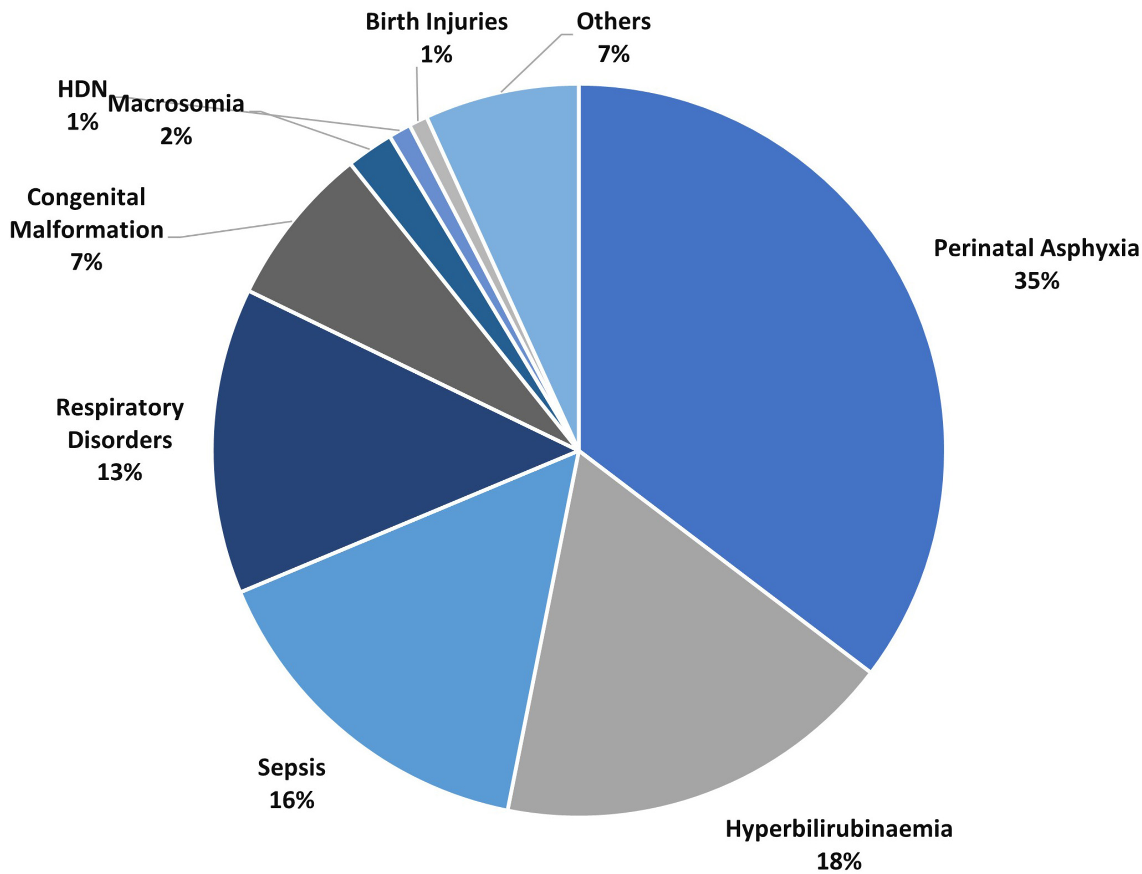

FIGURE 2 | Morbidity pattern among 9,030 term babies.

DISCUSSION

The present study involved 14,760 newborns over 12 years, and it represents one of the most extensive data sets from tertiary health facilities in a developing country. From the literature search, the closest report regarding the audit of newborn care in a tertiary health center from a developing nation was the retrospective study involving 7,225 newborns over 10 years by Owa and Osinaike (32) in Southwestern Nigeria. This extensive database from a facility that provides considerable access to primary and secondary health care will significantly represent the spectrum of neonatal conditions prevalent in the study site. The precision of diagnosis will also be better than the verbal autopsy techniques, which have been shown to have some challenges, mainly when carried out by non-physicians (31, 32).

Of importance for a study from Nigeria, a middle-income country, causes of morbidity and mortality in this study are reported separately for term and preterm neonates. In prior studies, prematurity itself has often been labeled as the "cause" of morbidity or mortality but our approach sheds additional light on how causes of morbidity and mortality vary between a baby who is term as compared to preterm. The third goal of the SDG is concerned with reducing neonatal mortality to less than 20 per thousand live births, which underscores the need to identify the peculiar characteristics of preterm babies as part of efforts toward meeting this goal. Unfortunately, the WHO annual health statistics and other health indices data continue to lump all causes of newborn deaths together (33). From the robust data in this study, a critical separation of the causes of death into two main categories has allowed the separation of burden and causes of death in preterm babies from term babies. It is expected to serve as a critical reference in tracking the load of preterm babies and the distribution of their various morbidities/mortalities.

The term babies' admissions trend showed a steady rise from 8.3% in 2007 to a peak at 10.7% in 2009 before a steady decline to 5.7% in 2016. Within the period, the annual percentage mortality compared with the admission of the same year showed a decrease from 15.7% in 2007 to 9.4% in 2018. This finding is also in tandem with Nigeria's demographic health survey that showed a progressive decline in neonatal mortality in Nigeria (4). However, our results contrast with a similar study in Tanzania, where the mortality rate stagnated over 10 years (34). The significant reduction in mortality among term babies observed between 2013–2018 and 2007–2009 could be attributed to some factors. As part of the movement of the teaching hospital to the current definitive site, the NICU was also relocated at the end of 2009 to a more purpose-built facility that is better aligned with the labor and delivery unit, improved oxygen supply, and acquisition

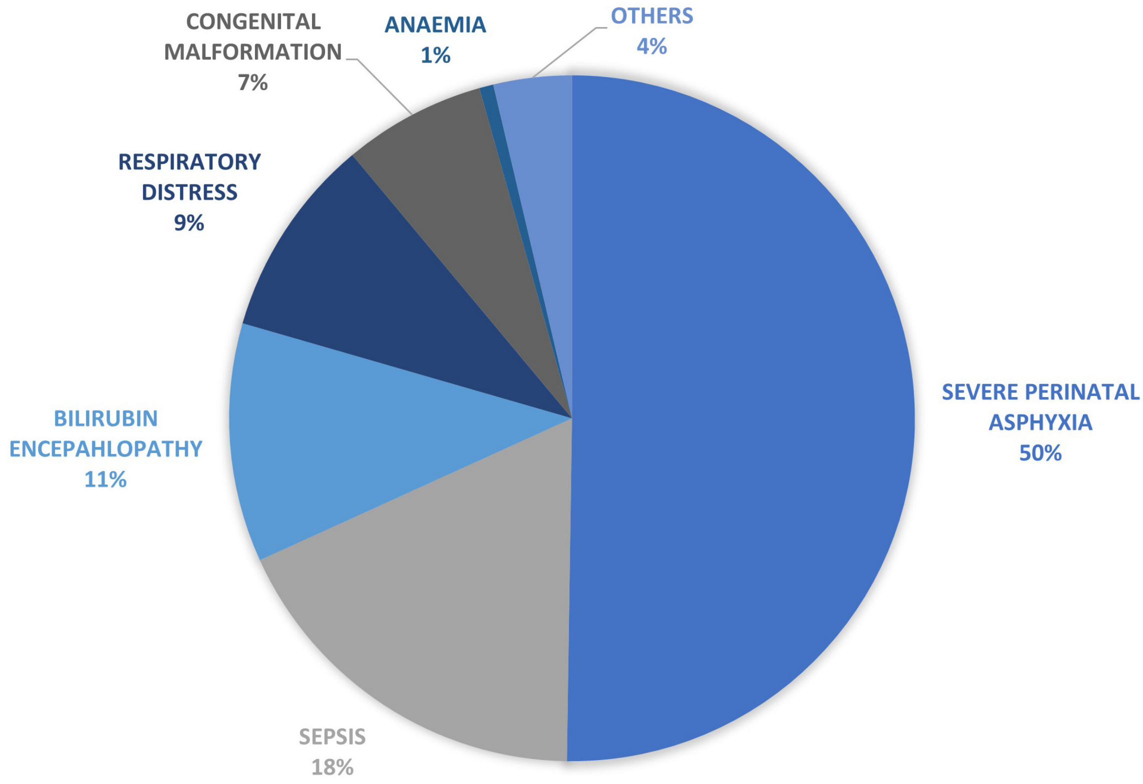

FIGURE 3 | Cause of mortality among term babies.

of a modern set of incubators and ventilators through federal government's VAMED Engineering Equipment Program. The set of modern incubators complemented existing digitally re-cycled old incubators, which have been documented to improve neonatal outcomes significantly (27).

The data on morbidity among term babies revealed that perinatal asphyxia (35%), hyperbilirubinemia (18%), neonatal sepsis (15%), and respiratory distress (14%) were the leading causes of admissions. Congenital malformations, often unreported, were ranked as the 5th most common cause of admissions (2). While virtually all studies that audited neonatal morbidity and mortality have reported perinatal asphyxia as the leading cause of newborn admissions, only a few have reported the burden of neonatal jaundice (14, 15) This has often led to jaundice being a "hidden cause of neonatal morbidity/mortality." This is not unexpected as most studies did not separate term from preterm babies or were limited by study sample size (18, 35). However, in keeping with the findings of this study are a few studies that examined the actual burden of jaundice among newborns and documented higher prevalence (as high as 25.6 to 45.6%) among newborn admissions (36, 37).

The causes of death among term babies showed that perinatal asphyxia still ranks first, keeping with global causes of newborn deaths in developing countries (2). This was followed by neonatal sepsis, bilirubin encephalopathy, respiratory disorders, congenital malformation, and hematological problems. A systematic review of the burden of neonatal death in the southeast Asian nations showed the leading cause of death as birth asphyxia, neonatal sepsis, and congenital malformation with the absence of hyperbilirubinemia (38). This study shows neonatal jaundice was ranked the third most common cause of death after perinatal asphyxia and neonatal sepsis. Unfortunately, the global efforts focus more on perinatal asphyxia and sepsis, while hyperbilirubinemia remains a cause for concern (39). The pie-chart showing mortality (**Figure 2**) also demonstrated that congenital malformation was responsible for 7% of deaths, which seems relatively high. Still low compared to figures from Cameroon, which recorded a 10.5% mortality rate (40). These differences could be attributed to the fact that the Cameroon study did not separate preterm from term babies.

From the present study, the trend of annual preterm admissions showed a steady rise with dips in 2011 and 2016. This can be attributed to the hospital's relocation from the old site to the permanent site and various industrial actions that occurred during the period. Furthermore, the chi-square for trend showed significant improvement in the survival rate among this set of newborns. This can be attributed to the improved newborn care and our ability to adapt where there are challenges (27).

The leading causes of admission among preterm babies (**Figure 3**) were perinatal asphyxia, neonatal sepsis, respiratory distress, hyperbilirubinemia, anemia of prematurity, intraventricular hemorrhage, and congenital malformation, respectively. This is in contrast to the order of causes of admission (respiratory distress, sepsis, hyperbilirubinemia, and perinatal

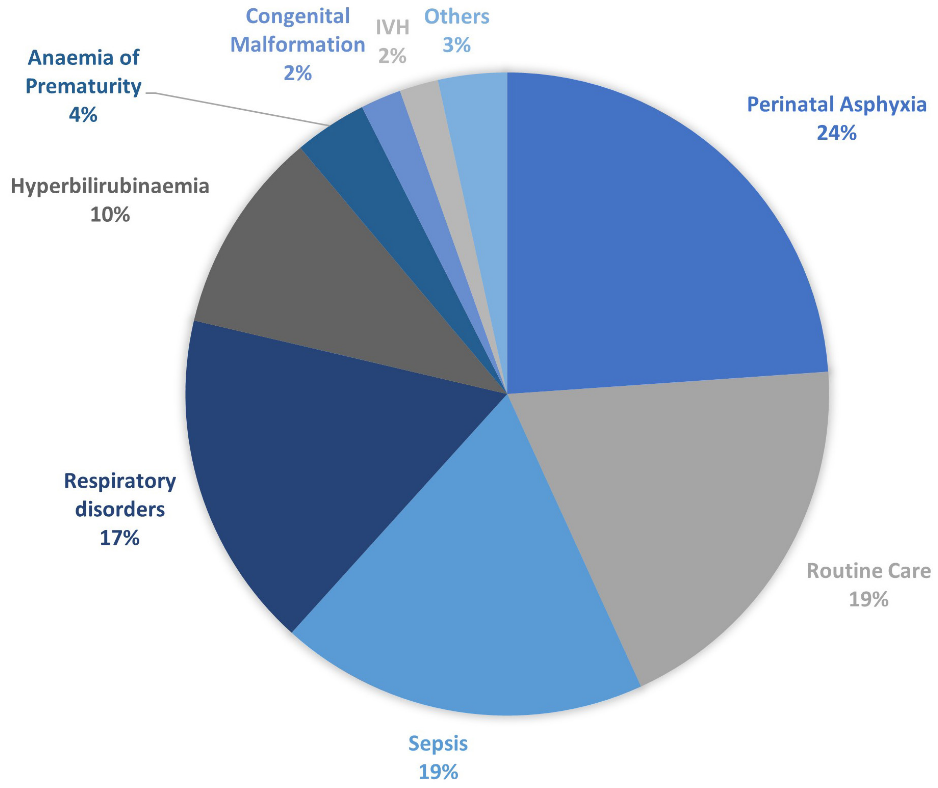

FIGURE 4 | Morbidity pattern among 4,938 preterm babies.

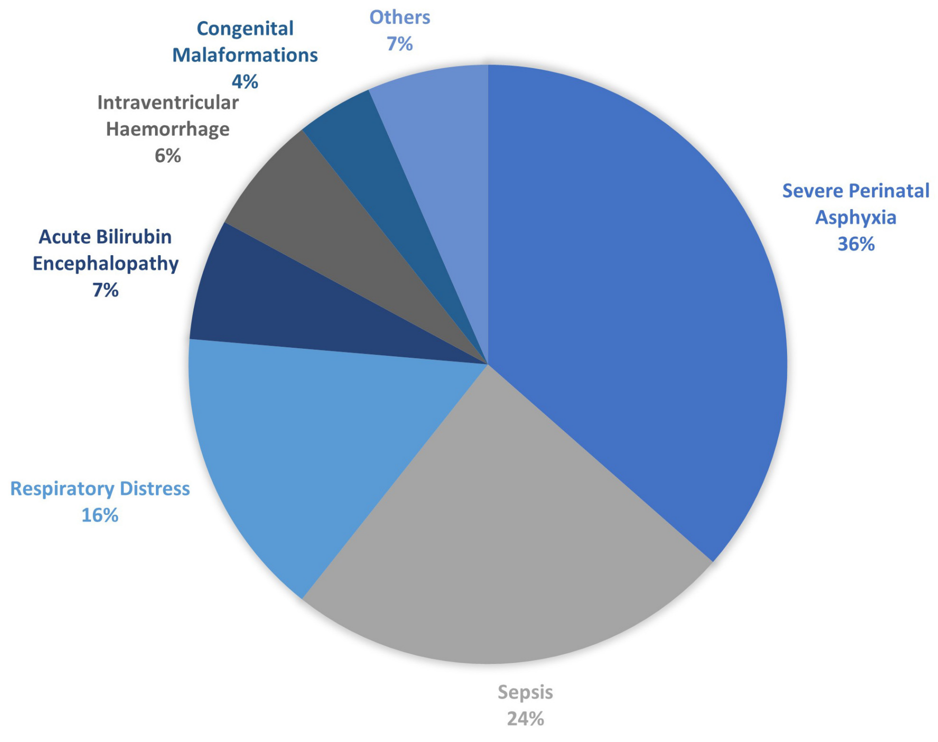

FIGURE 5 | Cause of mortality among preterm babies.

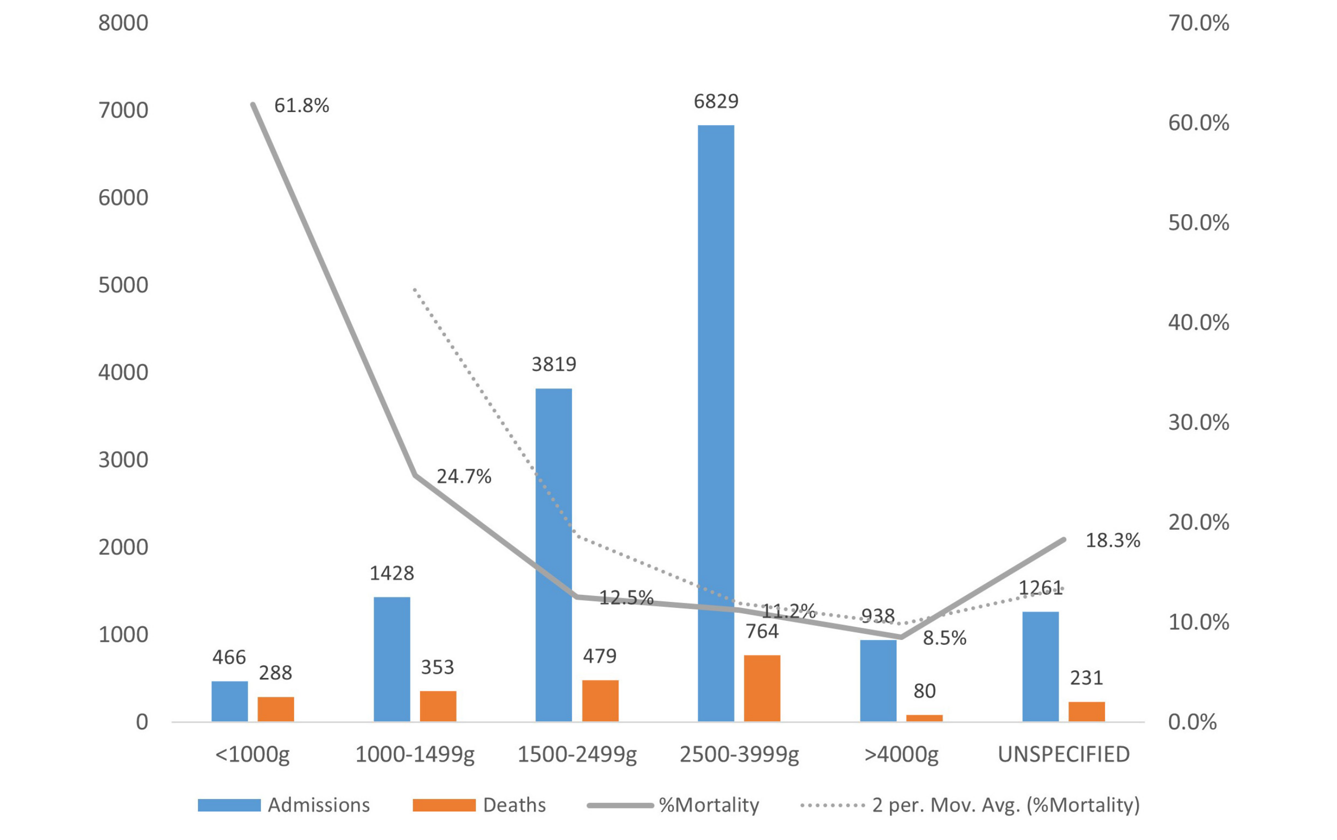

FIGURE 6 | Trend in morbidity and mortality based on birthweight.

asphyxia) reported by Kunle-Olowu et al. (40) at a tertiary center in South-South Nigeria. The differences in the order of causes of admission could be partly attributed to the relatively small size of preterm babies (41) studied by Kunle-Olowu et al. (40) compared to the subjects in the present study. Babies admitted for routine prematurity care included those whose gestational age was less than 32 weeks and weighed less than 1,500 g who were offered care to prevent problems associated with prematurity. Unsurprisingly, neonatal sepsis ranked second as the leading cause of admissions which is not unexpected considering their vulnerability to infections. The leading causes of death among the preterm (**Figure 3**) were perinatal asphyxia, sepsis, respiratory distress, and intraventricular hemorrhage. Though limited in distribution cause of death, a study in Bangladesh identified perinatal asphyxia and sepsis as the leading cause of preterm babies' death, which is in keeping with our observation (42). This study has shown that perinatal asphyxia is the leading cause of death among newborns, keeping with global findings. In contrast, Ugwu (42) documented respiratory complications as the number one cause of death and perinatal asphyxia as the fourth leading cause of death. The differences in the findings could be because the most common preterm problem may present with respiratory distress, which may lead to classification as a respiratory disorder. While respiratory diseases such as respiratory distress syndrome are common in preterm, various clinical conditions such as aspiration, perinatal asphyxia with pulmonary hypertension, and infection may present with respiratory distress in preterm babies after birth (46).

The birth weight remained a strong determinant of survival of newborns, and low birth weight babies tend to have higher mortality than other weight categories, which is in keeping with a multi-countries study on neonatal death (12). The relatively low survival rate (38%) of extremely low birth weight babies may be attributed to the high rate of complications in this weight category. Furthermore, this study's finding of least mortality due to macrosomia seems unexpected considering that macrosomic babies are a high-risk group. However, the results could be explained because most macrosomic babies tend to be delivered at a health facility with early admissions. Also supporting the findings was the recent work of Spogmai et al. (43), who found that macrosomia was associated with a generally protective effect against perinatal death.

The survival rate of 36% among babies less than 28 weeks from this study showed that 3–4 of 10 babies survived. Thus, the need for a review of the cut-off gestation age of 28 weeks used to define the period of viability in most developing countries. The least percentage of mortality was also observed at the gestational age of 34–36 weeks which is similar to the findings by Klingenberg et al. (44) at a tertiary health facility in Tanzania. The low mortality among gestational age 34–36 weeks may be related to the fact these babies have achieved lung maturity, a birth weight that favors less difficulty at delivery, and lesser

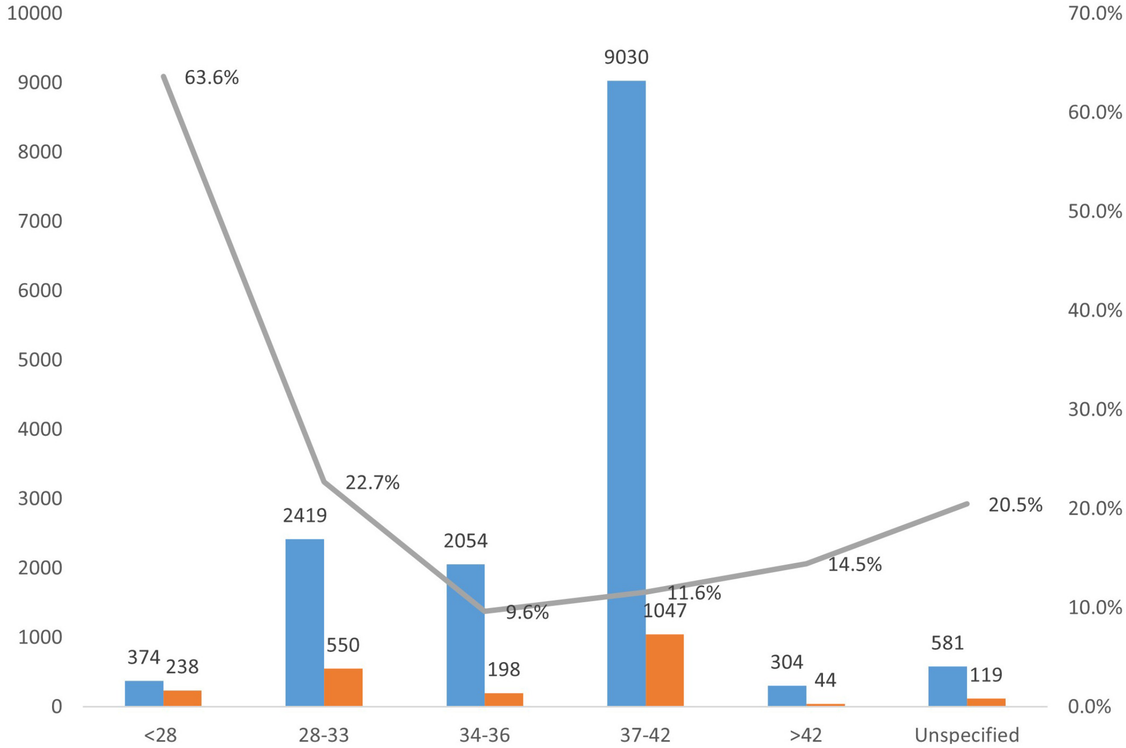

FIGURE 7 | Trend in morbidity and mortality based on gestational age.

problems associated with prematurity (45). Our findings are consistent with the call by Amadi et al. (26) to use frugal remedies for lowering facility-based neonatal mortality and morbidity in Nigeria. Additionally, Mokuolu et al. (24) provide a rational basis for improved selection and quality of care for pregnant women at risk of preterm delivery.

CONCLUSION

The study demonstrated gains in using several pragmatic approaches to the care of newborns despite resource challenges with a decline in the mortality rate over 12 years. In addition, hyperbilirubinemia remains among the leading cause of neonatal morbidity and mortality in our environment. This study also shows that pragmatic approaches remain crucial to the SDG objective of reducing newborn mortality. A unique contribution is reporting specific causes of morbidity and of mortality in two groups—for term babies and also for premature babies. This approach is more informative than simply listing "prematurity" as the cause and will inform future interventions which may differ by gestational age.

Recommendation

There is the need to build on these gains with the adoption of awareness campaigns to improve neonatal morbidity and mortality at various levels of delivery, greater penetration of essential care of the newborn in the community and lower level of health facilities, timely referrals, and building the skills of frontline pediatricians and neonatologists on ventilatory support, parenteral nutrition, and neonatal resuscitation.

Limitations

There were years when the hospital experienced prolonged strike actions that disrupted services. While the neonatal unit never stopped operating during those periods, a significant reduction in the number of babies seen and admissions was selectively related to the very severe conditions. This may have caused minor distortions in the denominators used for those years. In addition, 186 babies were delivered outside the hospital and presented late with unknown birth weights. We computed the weight categorization from the weight taken at the point of admission.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Ilorin Teaching Hospital Ethical Review Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

OM and OA designed the study and developed the initial draft of the manuscript. All authors were part of the data collation and contributed to the review of the final manuscript.

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Emerging Antibiotic Resistance Patterns in a Neonatal Intensive Care Unit in Pune, India: A 2-Year Retrospective Study

Mubashir Hassan Shah[1†], Samuel McAleese[2†], Sandeep Kadam[3], Tushar Parikh[3], Umesh Vaidya[3], Sonali Sanghavi[4] and Julia Johnson[2,5]*

[1] Department of Pediatrics, Government Medical College, Srinagar, India, [2] Division of Neonatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3] Division of Neonatology, Department of Pediatrics, King Edward Memorial Hospital & Research Centre, Pune, India, [4] Department of Microbiology, King Edward Memorial Hospital & Research Centre, Pune, India, [5] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

Objective: Treating neonatal bloodstream infections and meningitis in South Asia remains difficult given high rates of antimicrobial resistance (AMR). To evaluate changing epidemiology of neonatal infections, we assessed pathogen-specific and clinical features of culture-proven infections in neonates admitted to a neonatal intensive care unit (NICU) in Pune, India.

Materials and Methods: This retrospective cohort study was performed in the King Edward Memorial Hospital and Research Center NICU over 2 years between January 1, 2017 and December 31, 2018. We included all neonates admitted to the NICU with positive blood or cerebrospinal fluid cultures. Demographic, clinical, and microbiologic data were collected from the medical record. We reviewed antimicrobial susceptibility testing (AST) of all isolates.

Results: There were 93 culture-positive infections in 83 neonates, including 11 cases of meningitis. Fifteen (18%) neonates died. Gram-negative pathogens predominated (85%) and AST showed 74% resistance to aminoglycosides, 95% resistance to third/fourth generation cephalosporins, and 56% resistance to carbapenems. Resistance to colistin was present in 30% of *Klebsiella pneumoniae* isolates. Birth weight <1,000 g [odds ratio (OR) 6.0, $p < 0.002$], invasive respiratory support (OR 7.7, $p = 0.001$), and antibiotics at the time of culture (OR 4.2, $p = 0.019$) were associated with increased risk of mortality. Rates of AMR to all major antibiotic classes were similar between early onset and late onset infections. There was no association between carbapenem resistance and mortality.

Conclusion: In our NICU in India, there are high rates of AMR among Gram-negative pathogens that are predominantly responsible for infections. Given higher colistin resistance in this cohort than previously reported, hospitals should consider routinely testing for colistin resistance.

Keywords: neonatal sepsis, bloodstream infection, meningitis, antimicrobial resistance, colistin resistance

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K. C. Ashish,
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Ketil Størdal,
University of Oslo, Norway
Prajwal Paudel,
Paropakar, Nepal

Correspondence:
Samuel McAleese
smcalee1@jh.edu

† These authors share first authorship

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INTRODUCTION

Neonatal sepsis causes a large proportion of all neonatal deaths worldwide (1). India reports higher rates of neonatal infections than other low- and middle-income countries (LMIC), and a recent review of neonatal infections in India reported a case fatality rate of 50% for culture-positive sepsis (2, 3). Compounding the difficulty and complexity of treating neonatal sepsis is antimicrobial resistance (AMR); as antibiotic use has increased and broader spectrum antibiotics are used more frequently, AMR has risen (4). Previously published longitudinal data from our neonatal intensive care unit (NICU) in western India from 2006 to 2008 already showed a worrying increase in multidrug-resistant (MDR) infection over the 2-year study period as well as persistently high rates of cephalosporin and carbapenem resistance (5). A more recent systematic review from 2019 on AMR in neonatal sepsis in South Asia (including 69 studies from India) shows that these challenges are ongoing and more widespread (6). This review reported rates of resistance between 67 and 86% to first-line drugs recommended by the World Health Organization (WHO), such as ampicillin, gentamicin, and third-generation cephalosporins, as well as high (50–70%) degree of MDR in isolates throughout India and South Asia.

AMR surveillance studies guide institutional infection prevention practices, help national efforts to standardize recommendations, and inform future implementation research. These studies can also inform practices outside the regions and countries being studied. Human travel and globalization have contributed to the global spread of select mutations that confer colistin resistance, reinforcing the notion that AMR is not only a local or regional concern (7). Given the worsening trends in AMR, ongoing surveillance is vital to better assess risk factors for infection and the appropriateness of commonly used empiric antibiotic regimens. The objective of this study was to evaluate pathogen-specific and clinical features of culture-proven infections in neonates admitted to the NICU at a tertiary care healthcare facility in western India.

MATERIALS AND METHODS

Patient Selection and Clinical Data

This retrospective cohort study was conducted at King Edward Memorial Hospital & Research Center (KEMHRC), a 550-bed multispecialty tertiary care teaching hospital in urban Pune, India, with a 50-bed Level III NICU. As part of the largest non-governmental hospital in Pune and a major referral center for the state of Maharashtra, the Department of Obstetrics and Gynecology at KEMHRC performs over 3,000 deliveries annually including high-risk deliveries. Approximately 1,000 infants—predominantly born at KEMHRC—are admitted to the NICU annually, although the NICU also serves as a referral center for smaller facilities throughout Maharashtra. This two-year study included all neonates admitted to the NICU between January 1, 2017, and December 31, 2018 with a documented positive culture from blood or cerebrospinal fluid (CSF). Culture specimens were collected and processed according to routine laboratory standards in KEMHRC's nationally accredited microbiology laboratory. Data were manually extracted from the hospital's electronic medical record using a standardized case report form. Demographic, birth, and clinical data were collected, including gestational age, birth weight, presence of central line at time of positive culture, relevant clinical diagnoses, and disposition. Microbiologic data were collected, including organism isolated, results of antibiotic susceptibility testing (AST), and time to culture positivity.

Diagnostic and Microbiological Criteria

We examined all culture-proven infections in neonates. Culture-proven infections were defined as positive blood or CSF culture. Blood and CSF samples of minimum 1 ml were collected using aseptic technique; samples were immediately transported to the in-hospital laboratory for automated processing using the BD FX™ system (BD, Franklin Lakes, NJ, USA). Cultures that tested positive were subcultured on blood agar, MacConkey agar, and chocolate agar (CSF cultures only). Positive cultures with the same organism from both blood and CSF were considered as part of the same culture-positive infection. Multiple positive cultures from the same neonate were considered part of the same culture-positive infection unless a distinct organism was isolated, or the culture was drawn more than 7 days after the prior culture. Early onset blood stream infection (BSI) was defined as positive blood culture in the first 72 h of life, and early onset meningitis was defined as positive CSF culture in the first 72 h of life. Late onset BSI and meningitis were defined as positive culture from blood or CSF, respectively, after 72 h of life. Necrotizing enterocolitis (NEC) was defined as stage II or greater on modified Bell's criteria (8). Retinopathy of prematurity (ROP) was defined as any stage per International Committee for Classification of Retinopathy of Prematurity (ICROP) criteria (9). Intraventricular hemorrhage was defined according to the Papile grading classification (10). AST for all antibiotics was performed on the Vitek 2® system (BioMérieux, Inc, Hazelwood, MO, USA). Susceptibility testing results were interpreted according to minimum inhibitory concentration breakpoints set by the Clinical and Laboratory Standards Institute (CLSI, Malvern, PA, USA). Antibiotic resistance was defined as resistance or intermediate susceptibility on AST; resistance to a class of antibiotics was defined as resistance or intermediate susceptibility to any antimicrobial in that class.

Statistical Analysis

Descriptive analysis was performed on the study population. Statistical analysis was performed with Stata 15.1 (StataCorp, College Station, TX, USA). Univariate regression using a Pearson χ^2-test was used to assess the associations between clinical risk factors, carbapenem resistance, and mortality.

Ethics Statement

This study was approved by the KEMHRC Ethics Committee (ID No. 2108).

RESULTS

There were 113 positive cultures during the study period, 101 from blood samples and 12 from CSF samples (see **Figure 1**). Three blood samples were excluded as contaminants [*Brevundimonas* spp. ($n = 1$), *Granulicatella* spp. ($n = 1$), *Rhizobium* spp. ($n = 1$)]. Six blood cultures and one CSF culture from four neonates were positive within 7 days of a prior culture from the same source with the same organism and were considered as part of the same culture-positive infection. Of 11 remaining positive CSF cultures, 10 resulted with the same pathogen as a positive blood culture drawn on the same day and were considered part of the same culture-positive infection. One infant had a positive CSF culture without concurrent positive blood culture. After exclusions, there were 93 culture-positive cases of BSI or meningitis in 83 neonates. Fifty-three percent (49/93) of all infections occurred in males and 84% (78/93) occurred in inborn neonates (**Table 1**). The median age at birth in completed gestational weeks was 31 [interquartile range (IQR) 29–33] and the median birth weight was 1,340 g (IQR 1,040–1,750). Twenty percent (17/83) of neonates were extremely low birth weight (ELBW, or <1,000 g at birth). Thirty-one percent (26/83) of neonates required invasive ventilation during their hospitalization. Median length of stay was 29 days (IQR 15–41). Fifteen (18%) infants died. Three of four neonates (75%) with documented fungal infections died. Neonates with repeat infections were smaller at birth (median birth weight 1,028 g, IQR 863–1,265) and had prolonged hospitalizations (median length of stay 49 days, IQR 32–62). Of positive cultures from the same neonates, 50% (5/10) were unique infections with the same organism, but minimal changes to susceptibility patterns were noted on AST. The median time between unique infections for these neonates was 14 days (IQR 9–19).

The majority of infections were late onset (82%, 76/93) with a median age at time of positive culture of 7 days (IQR 4–11) (**Table 2**). Central lines were present at time of culture in 53% (49/93) of cases. Of infections with a central line present at time of positive culture, the median for total duration of central line use was 6 days (IQR 4–12). The median time to culture positivity (from incubation to growth) was 22 h (IQR 19–25).

Gram-negative infections were predominant (85%, 79/93) (**Table 3**). The most commonly isolated Gram-negative pathogens were *Klebsiella pneumoniae* (52% of all infections, 48/93), *Acinetobacter* spp. (15%, 14/93), and *Escherichia coli* (9%, 8/93). *Enterococcus faecalis* accounted for 60% of Gram-positive infections (6/10) and 6% of all infections (6/93). There were four fungal infections, all caused by *Candida albicans*.

Among the 10 neonates with meningitis, one neonate had two separate CSF infections (18 days apart). Neonates with meningitis were predominantly male (80%, 8/10); all 10 (100%) were premature. Of 11 cases of meningitis, 82% were late onset; the median day of life for a positive CSF culture was 10 days (IQR 4–20). Infants with meningitis had prolonged hospitalizations compared to the entire cohort (39 days, IQR 36–44). Only one (10%) neonate with meningitis died. Pathogens isolated from CSF cultures included *E. faecalis* ($n = 3$, 27%), *K. pneumoniae* ($n = 3$, 27%), *Acinetobacter* spp. ($n = 2$, 18%), *Serratia marcescens* ($n = 1$, 9%), *Elizabethkingia* spp. ($n = 1$,

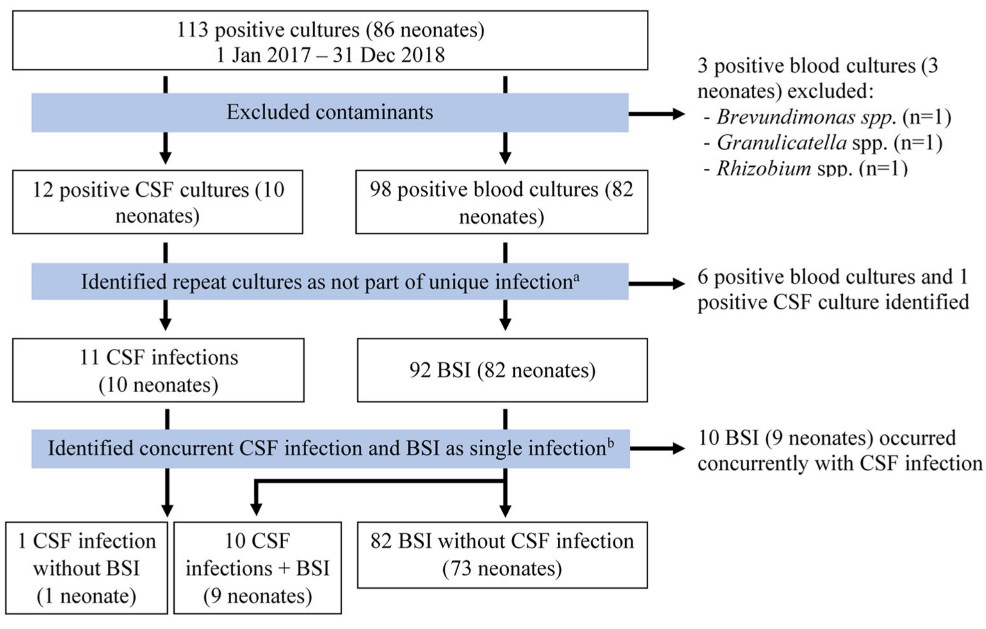

FIGURE 1 | Flow diagram used to identify unique infections. Meningitis and CSF infection were used interchangeably. [a]Multiple positive cultures from the same neonate were considered part of the same culture-positive infection unless a distinct organism was isolated, or the culture was drawn more than 7 days after the most recent positive culture. [b]Positive cultures with the same organism from both blood and CSF were considered as part of the same culture-positive infection. BSI, bloodstream infection; CSF, cerebrospinal fluid.

TABLE 1 | Clinical and demographic characteristics of neonates with culture-positive bloodstream infections or meningitis.

	BSI only (*n* = 73)	Meningitis (*n* = 10)	Total (*n* = 83)
Maternal age in years, median (IQR)	28 (25–32)	28 (24–30)	28 (24–32)
Female sex, *n* (%)	39 (53)	2 (20)	41 (49)
Gestational age at birth in weeks, median (IQR)	32 (29–33)	30 (29 –31)	31 (29–33)
Premature (<37 weeks), *n* (%)	64 (88)	10 (100)	74 (89)
Birth weight in grams, median (IQR)	1,340 (1,040–1,750)	1,334 (1,200–1,367)	1,340 (1,040–1,750)
ELBW, *n* (%)	16 (22)	1 (10)	17 (20)
IUGR[a], *n* (%)	18 (25)	1 (10)	19 (23)
Inborn, *n* (%)	62 (85)	8 (80)	70 (84)
Vaginal delivery, *n* (%)	36 (49)	8 (80)	44 (53)
Resuscitation at delivery[b], *n* (%)	25 (34)	2 (20)	27 (33)
Premature rupture of membranes, *n* (%)	19 (26)	1 (10)	20 (24)
Intrapartum maternal fever (38.5°C or higher), *n* (%)	2 (3)	0 (0)	2 (2)
Antenatal maternal steroid administration, *n* (%)	43 (59)	6 (60)	49 (59)
Meconium-stained amniotic fluid, *n* (%)	1 (1)	0 (0)	1 (1)
Any respiratory support, *n* (%)	49 (67)	4 (40)	53 (64)
Invasive respiratory support, *n* (%)	23 (32)	4 (40)	27 (33)
Any IVH[c], *n* (%)	13 (18)	2 (20)	15 (18)
Severe IVH (Grade 3 or 4)[c], *n* (%)	1 (1)	1 (10)	2 (2)
ROP[d], *n* (%)	10 (14)	0 (0)	10 (12)
NEC[e], *n* (%)	6 (8)	1 (10)	7 (8)
Hospital stay in days, median (IQR)	25 (14–37)	39 (36–44)	29 (15–41)
Died, *n* (%)	14 (19)	1 (10)	15 (18)

Clinical and demographic characteristics of neonates with culture proven infection. A total of 83 neonates had culture-proven infections during the study timeframe. Neonates with multiple distinct episodes of infection were included only once. [a]IUGR defined as less than 10th percentile on gestational age appropriate growth curve. [b]Resuscitation at delivery defined as need for positive pressure ventilation. [c]Intraventricular hemorrhage defined according to Papile grading criteria (10). [d]Retinopathy of prematurity defined as any stage per International Committee for Classification of Retinopathy of Prematurity criteria (9). [e]NEC defined as stage II or greater on modified Bell's criteria (8). BSI, bloodstream infection; ELBW, extremely low birth weight; IQR, interquartile range; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

TABLE 2 | Characteristics of culture-positive infections in early onset and late onset infections.

	Early onset (*n* = 17)	Late onset (*n* = 76)	Total (*n* = 93)
Age at positive culture in days[a], median (IQR)	2 (1–3)	8 (6–14)	7 (4–11)
Central line at time of culture, *n* (%)	5 (29)	44 (58)	49 (54)
Total duration of central line[b], median (IQR)	3 (3–4) *n* = 5	8 (4–13.5) *n* = 44	6 (4–12) *n* = 49
Antibiotics at time of culture, *n* (%)	8 (47)	38 (50)	46 (49)
Time to positive culture from incubation in hours, median (IQR)	22 (19–28)	22 (19.5–24.5)	22 (19–25)

Clinical characteristics related to culture-positive infections in neonates, separated by early onset and late onset infections. Early onset infections were defined as occurring within 72 h of birth and late onset infections were defined as occurring after 72 h of life. [a]Date of birth reported as day of life 1. [b]Total duration of central line reflects total duration of central line presence, not duration at time of culture. IQR, interquartile range.

9%), and *Moraxella lacunata* (*n* = 1, 9%). Only one infant, who developed *S. marcescens* meningitis on day of life three, did not have concurrent BSI with the same organism.

Among pathogens causing BSI or meningitis, AMR was common. For all Gram-negative isolates, resistance to commonly used empiric antibiotic classes such as aminoglycosides and third-generation cephalosporins was reported in 74% (57 of 77 isolates tested) and 95% (73/77), respectively (**Table 4**). Gentamicin was less effective than amikacin; 67% (58/87) of samples were resistant to gentamicin compared to 26% (17/66) that were resistant to amikacin. Carbapenem resistance was 56% (42/75); resistance to fluoroquinolones was 91% (70/77). Resistance to colistin was reported in six of 44 isolates tested (14%), all six of which were *K. pneumoniae*, corresponding to 30% colistin resistance for the most commonly isolated pathogen in our cohort.

Resistance to carbapenems was seen in 46% (6/13) of early onset infections and 58% (36/62) of late onset infections. Although rates of resistance to aminoglycosides were similar between early onset and late onset infections (67%, 11/16 vs. 74%, 53/72, respectively), this similarity was less notable for amikacin. Resistance to amikacin was seen in 8% (1/12) early onset infections and 29% (16/55) late onset infections. Rates

TABLE 3 | Distribution of pathogens in early onset and late onset culture-positive infections.

	Early onset (n = 17)	Late onset (n = 76)	Total (n = 93)
Gram-negative organisms, n (%)	14 (82)	65 (86)	79 (85)
Klebsiella pneumonia	7 (41)	41 (54)	48 (52)
Acinetobacter spp.	2 (12)	12 (16)	14 (15)
Escherichia coli	2 (12)	6 (8)	8 (9)
Elizabethkingia spp.	0 (0)	3 (4)	3 (3)
Serratia marcescens	1 (6)	2 (3)	3 (3)
Enterobacter cloacae	0 (0)	1 (1)	1 (1)
Bulkholderia cepacia	1 (6)	0 (0)	1 (1)
Moraxella lacunata	1 (6)	0 (0)	1 (1)
Gram-positive organisms, n (%)	2 (12)	8 (11)	10 (11)
Enterococcus faecalis	1 (6)	5 (7)	6 (6)
Coagulase-negative *Staphylococcus* spp.	1 (6)	2 (2)	3 (3)
Staphylococcus aureus	0 (0)	1 (1)	1 (1)
Fungal organisms, n (%)	1 (6)	3 (4)	4 (4)
Candida albicans	1 (6)	3 (4)	4 (4)

Pathogen distribution for all culture-positive infections, identified by early or late onset infections. Early onset infections were defined as occurring within 72 h of birth and late onset infections were defined as occurring after 72 h of life.

TABLE 4 | Antimicrobial susceptibility testing for culture-positive Gram-negative infections.

	Aminoglycoside[a] resistance (n = 78)	Fluoroquinolone[b] resistance (n = 77)	3rd/4th generation cephalosporin[c] resistance (n = 77)	Carbapenem[d] resistance (n = 75)	Colistin resistance (n = 41)
Gram-negative organisms, n resistant/isolates tested (%)	57/78 (73)	70/77 (91)	72/77 (94)	42/75 (56)	6/41 (14)
Klebsiella pneumoniae	32/47 (68)	43/46 (93)	45/46 (98)	26/46 (57)	6/20 (30)
Acinetobacter spp.	13/14 (93)	13/14 (93)	13/14 (93)	12/13 (92)	0/14 (0)
Escherichia coli	8/8 (100)	8/8 (100)	8/8 (100)	0/8 (0)	0/5 (0)
Elizabethkingia spp.	3/3 (100)	2/3 (67)	3/3 (100)	3/3 (100)	–
Serratia marcescens	1/3 (33)	3/3 (100)	2/3 (67)	1/2 (50)	–
Enterobacter cloacae	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Bulkholderia cepacia	0/1 (0)	1/1 (100)	1/1 (100)	0/1 (0)	–
Moraxella lacunata	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)

Antimicrobial susceptibility testing reported by pathogen. Resistance defined as intermediate susceptibility or resistance. Resistance to a class of antibiotics described as resistance to one or more antibiotics tested in that class. For infants with identical pathogens identified from positive CSF and blood cultures on the same day, AST testing reported only once. Percentages calculated with number of resistant isolates as numerator and number of isolates tested as denominator. Dashes indicate testing was not done on these isolates. [a]Aminoglycoside antibiotics tested were amikacin and gentamicin. [b]Fluoroquinolone antibiotics tested were ciprofloxacin and levofloxacin. [c]3rd and 4th generation cephalosporin antibiotics tested were cefoperazone/sulbactam, ceftazidime, ceftriaxone, and cefepime. [d]Carbapenem antibiotics tested were doripenem, meropenem, and imipenem.

of resistance to 3rd/4th generation cephalosporins (86%, 12/14 vs. 95%, 61/64), fluoroquinolones (93%, 13/14 vs. 91%, 58/64), and colistin (14%, 1/7 vs. 14%, 5/37) were similar in early onset infections and late onset infections.

Although Gram-negative infections were predominant, there were 10 Gram-positive infections and four blood cultures positive for *C. albicans*. All *E. faecalis* samples were susceptible to vancomycin and linezolid, but resistant to clindamycin. The four fungal isolates were susceptible to all antifungal therapies tested (amphotericin-B, caspofungin, fluconazole, flucytosine, and micafungin).

Among clinical characteristics of neonates, only ELBW [odds ratio (OR) 6.0, confidence interval (CI) 1.9–18.7, $p = 0.002$], invasive respiratory support (OR 7.7, CI 2.4–24.9, $p = 0.001$), and antibiotic use at time of culture (OR 4.2, CI 1.3–14.2, $p = 0.019$) were associated with an increased risk of mortality (**Table 5**). There were no deaths among neonates with colistin-resistant infections. Carbapenem resistance was not associated with mortality among all neonates. A sub-analysis of only preterm neonates ($n = 74$) was done. Clinical characteristics and AST testing of the 84 infections were similar compared to the entire cohort. In preterm infants, the presence of a central

TABLE 5 | Association of clinical characteristics and carbapenem resistance with mortality.

	Mortality		
	OR	**95% CI**	***p*-value**
Prematurity	0.23	0.05–0.96	0.05
Male sex	0.57	0.20–1.64	0.30
Antenatal steroids	0.61	0.21–1.76	0.36
Intrapartum maternal fever	*	*	*
Meconium-stained fluids at birth	*	*	*
ELBW	**6.0**	**1.93–18.66**	**0.002**
Vaginal delivery	1.36	0.47–3.93	0.58
Inborn	0.65	0.13–3.17	0.59
Invasive respiratory support	**7.73**	**2.40–24.91**	**0.001**
PROM	0.81	0.24–2.75	0.73
Resuscitation at birth	1.9	0.66–5.60	0.23
Central line at time of culture	2.6	0.81–7.88	0.11
IUGR	1.45	0.45–4.68	0.54
Antibiotics at time of culture	**4.23**	**1.26–14.19**	**0.02**
Gestational diabetes	0.47	0.05–3.94	0.48
Gestational hypertension	0.99	0.33–2.97	0.98
Carbapenem resistance	1.52	0.46–5.09	0.49
Doripenem resistance	0.70	0.15–3.2	0.64
Meropenem resistance	0.94	0.29–2.99	0.91
Imipenem resistance	1.47	0.44–4.92	0.53

*Univariate analysis for baseline clinical characteristics, carbapenem resistance, and mortality. *Odds ratios unable to be calculated in these cases given small sample sizes and lack of neonates in all groups. CI, confidence interval; ELBW, extremely low birth weight; IUGR, intrauterine growth restriction; OR, odds ratio; PROM, premature rupture of membranes. Bold values are used to denote associations with p-values <0.05.*

line was also associated with mortality (OR 5.4, CI 1.1–25.8, $p = 0.037$).

DISCUSSION

Gram-negative infections predominate in our study, with 52% of all infections caused by *K. pneumoniae* and 14% caused by *Acinetobacter* spp. This epidemiologic profile mirrors prior hospital data reported in India where Gram-negative infections (especially *K. pneumoniae* and *Acinetobacter* spp.) account for 60–70% of all culture proven infections in neonates admitted to NICUs (3, 6). The high rate of *K. pneumoniae* infections in our study aligns with prior data from our institution (41% in 2006–2008) (5).

This study includes detailed AST data from a large number of isolates. Unfortunately, we report a high incidence of AMR to commonly used and broad-spectrum antibiotics. The majority of isolates were resistant to third-generation cephalosporins, aminoglycosides, and carbapenems. Resistance to carbapenems varied widely depending on the organism isolated. *Acinetobacter* spp., a major health-care associated pathogen in India capable of acquiring resistance, was nearly universally resistant to carbapenems in our study (11). There were similar levels of resistance to all drugs within most antibiotic classes, with the exception of aminoglycosides; isolates showed more susceptibility to amikacin, compared to gentamicin. This discrepancy exists in other areas of India as well as in other LMIC countries (12–14). The high rate of resistance to gentamicin likely is influenced by widespread use driven by its inclusion as a first-line antibiotic for neonatal sepsis in the WHO's guidelines (15). Institutions such as our own, which are routinely using amikacin as the preferred aminoglycoside instead of gentamicin, may find themselves limited in the future as AMR to efficacious antibiotics increases with increased use. This highlights the need not only to select appropriate antibiotics, but to prioritize antimicrobial stewardship activities to reduce overall antibiotic use.

Rates of resistance to antibiotic classes or single agents (excepting amikacin) were similar among early onset infections and late onset infections. A higher rate of resistance to amikacin in late onset infections may suggest that nosocomial spread contributes to rising rates of AMR or that early exposure to amikacin confers resistance in later infections. Transmission of AMR infections may be driven by multiple reservoirs of transmission, including maternal colonization with community-acquired pathogens followed by vertical transmission or rapid colonization after birth and subsequent infection. Better understanding of the differences in epidemiology between early and late onset neonatal infections is required to direct infection prevention practices and antimicrobial stewardship initiatives. At KEMHRC, multidisciplinary infection prevention and control (IPC) efforts are supported by dedicated nursing staff and include a focus on staff education, hand-hygiene, environmental surveillance, and outbreak investigations.

Notably, a central line was present more often and used for longer durations in late-onset BSIs compared to early-onset BSIs. Our study was not designed to assess whether the reported BSIs were central-line associated blood stream infections, but highlights an opportunity for tailoring IPC practices. Central lines are a known risk factor for BSI and that risk changes over the lifetime of the central line. At KEMHRC, umbilical catheters are not used beyond 7 days of life, and infants with expected prolonged need for central access preferentially undergo peripherally inserted central catheter (PICC) placement. IPC practices should account for the different risks associated with different phases of central line use (insertion, compared to maintenance). Some universal practices which apply to all phases (and all patients) include effective hand hygiene before and after every patient encounter and aseptic technique when inserting or accessing a central line. Daily discussion of line necessity and prompt removal of central lines when appropriate is an integral component of central line associated BSI prevention (16).

Prior to the rise in difficult-to-treat, MDR infections, colistin, a polymyxin antibiotic with activity against Gram-negative infections, was routinely avoided given paucity of data in neonates and concerns for difficult pharmacokinetics, nephrotoxicity, and neurotoxicity (17, 18). In India, clinicians over the past 10 years are turning more frequently to colistin as part of routine practice (19). Worryingly, our study showed higher rates of colistin resistance (14% overall, 30% in *K. pneumoniae* isolates) than previously reported in the literature on neonates in India (0–10%) (3, 20–25). Polymyxins are classified as a "reserve" antibiotic class by the WHO (26). Unfortunately, there is mounting evidence that increased colistin use drives colistin resistance, especially in *K. pneumoniae.* Epidemiologic data from a 2017 report by the European Center for Disease Prevention and Control on polymyxin use in 30 European countries reported an association between total consumption of polymyxin antibiotics and resistance in *K. pneumoniae* (27). In studies of hospitalized adult patients, use of colistin was a risk factor for infection with colistin resistant *K. pneumoniae* and there are reports of patients developing colistin resistance during colistin therapy (28–30). More concerning, once resistance in *K. pneumoniae* isolates develops, resistant infections have been shown to spread rapidly *via* clonal spread and biofilm formation, including in neonates (31–34).

Limiting colistin use and effective IPC programs to prevent spread of resistance are necessary to prevent further increases in resistance. Even when colistin use is appropriately limited to MDR infections, how it is used can potentially create conditions that lead to increased resistance. While colistin monotherapy is traditionally used, some question whether a combination regimen that includes colistin with possible synergistic effects would be more effective or even protective against colistin resistance (35, 36). Adequate dosing in MDR infections remains key as sub-optimal dosing or prolonged therapy has been shown to increase the risk for acquired resistance, including in neonates (30). Addressing the rising trend in colistin resistance will require comprehensive approaches including stewardship programs, IPC programs, and improved education about colistin use. Important to all of these initiatives will be improved surveillance for colistin resistance. Colistin resistance was not universally tested for in our study. However, given the increased risk of emerging resistance, clinicians and microbiologists should consider routinely testing for colistin on AST.

Limitations for this study include its retrospective nature, focus on a single center in western India, and lack of confirmatory cultures for potential contaminant pathogens. In our study, *Brevundimonas* spp., *Granulicatella* spp., and *Rhizobium* spp. were excluded as likely contaminants. As prior case reports have reported true infections in neonates with these pathogens, we may have excluded potential real infections (37–39). Coagulase negative staphylococcus (CoNS) isolates were included as infections despite lack of confirmatory culture given the known role of CoNS as a neonatal pathogen, especially in late onset neonatal infections (40).

This study adds awareness to the growing concern about rising AMR in neonatal infections in India. The lack of narrow empiric regimens with adequate coverage for neonatal sepsis leads to clinicians using broader spectrum agents as empiric therapy, which in turn, leads to increasing resistance. As use of last-resort antibiotics increases, clinicians must remain vigilant in prescribing practices. Standardization of empiric antibiotic therapy, avoiding overlapping therapy, and timely reevaluation of the antibiotic regimen (including narrowing coverage when appropriate and stopping antibiotics in neonates with negative cultures) are practical areas of focus for neonatal practitioners. Strengthening IPC practices and antimicrobial stewardship programs will be paramount in reducing the burden of AMR neonatal sepsis in India and other LMIC.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by King Edward Memorial Hospital Research Center Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MS: conceptualization, methodology, data collection, and data management. SM: literature review, data analysis, and writing—original draft, review, and editing. SK: conceptualization.

TP: conceptualization and data collection. UV: project administration. SS: data collection. JJ: conceptualization, data analysis, and writing—review and editing. All authors have approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.864115/full#supplementary-material

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An Observational Study of Therapeutic Hypothermia and Factors Associated With Mortality in Late-Preterm and Term Neonates With Hypoxic-Ischemic Encephalopathy in a Middle-Income Country

Nem Yun Boo[1], Siew Hong Neoh[2], Seok Chiong Chee[3]*
for the Malaysian National Neonatal Registry

[1] Department of Population Medicine, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Bandar Sungai Long, Malaysia, [2] Department of Paediatrics, Hospital Tunku Azizah, Ministry of Health, Kuala Lumpur, Malaysia, [3] Department of Paediatrics, Selayang Hospital, Ministry of Health, Batu Caves, Malaysia

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Susan Coffin,
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****Correspondence:***
Nem Yun Boo
boony@utar.edu.my

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Objectives: To investigate the types of therapeutic hypothermia (TH) used and risk factors associated with mortality in late-preterm and term neonates (LPTN, gestation of ≥35 weeks) with hypoxic-ischemic encephalopathy (HIE) in a middle-income country.

Design: This was an observational retrospective cohort study.

Setting: A total of 44 neonatal intensive care units (NICUs) in the Malaysian National Neonatal Registry participated in the study.

Patients: All LPTN without major malformations and diagnosed to have HIE were included.

Main Outcome Measures: Number of in-hospital mortality, and types of TH used [no TH, TH using commercially available servo-controlled devices (SCDs), passive TH by exposing neonates to NICU's air-conditioned ambient temperature with/without the use of cooled gel packs (P±CGPs)].

Results: Of a total of 2,761 HIE neonates, 66.3% received TH. All NICUs provided TH; 55.4% NICUs had SCDs, which was administered to 43.6% (248/569) of severe, 51.6% (636/1,232) of moderate, and 18.6% (179/960) of mild HIE neonates. P±CGPs was used on 26.9% of severe, 33.4% of moderate, and 21.1% of mild HIE neonates. There were 338 deaths. Multiple logistic regression analysis showed that 5-min Apgar scores <5 (aOR: 1.436; 95% CI: 1.019, 2.023), Cesarean section (aOR: 2.335; 95% CI: 1.700, 3.207), receiving no TH (aOR: 4.749; 95% CI: 3.201, 7.045), TH using P±CGPs (aOR: 1.553; 95% CI: 1.031, 2.338), NICUs admitted <50 HIE cases (aOR: 1.898; 95% CI: 1.225, 2.940), NICUs admitted 50-<100 HIE cases (aOR: 1.552; 95% CI: 1.065, 2.260), moderate HIE (aOR: 2.823; 95% CI: 1.495, 5.333), severe HIE (aOR: 34.925, 95% CI: 18.478, 66.012), Thompson scores of 7–13 (aOR: 1.776; 95% CI: 1.023,3.082), Thompson scores of ≥14 (aOR: 3.641; 95% CI: 2.000, 6.629), pneumothorax (aOR: 3.435; 95% CI: 1.996, 5.914), and foreigners (aOR: 1.646; 95% CI: 1.006, 2.692) were significant risk factors associated with mortality.

Conclusion: Both SCD and P±CGP were used for TH. Moderate/severe HIE and receiving passive/no TH were among the risk factors associated with mortality.

Keywords: hypoxic-ischemic encephalopathy (HIE), therapeutic hypothermia (TH), late-preterm and term neonates, middle-income countries, risk factors of mortality

INTRODUCTION

Neonatal hypoxic-ischemic encephalopathy (HIE) is due to acute peripartum or intrapartum events causing cerebral ischemia and oxygen deprivation. In the subsequent 1–6 h, oxidative metabolism may be restored with partial recovery of cells or secondary energy failure may continue leading to an increase in cerebral inflammation and cell death. Untreated, cytotoxic edema, excitotoxicity, and secondary energy failure develop with further cell death, seizures, clinical deterioration, and death (1–3). Survivors with moderate and severe HIE often develop long-term neurological impairments (4).

Therapeutic hypothermia (TH) at a moderate core temperature of 33.5 ± 0.5°C, initiated within 6 h after birth and maintained for 72 h, has been shown to reduce cellular injuries and cell death. Meta-analysis of studies in high-income countries (HICs) reported improved survival, following TH in late-preterm and term neonates (LPTN, gestation of ≥35 weeks) with moderate and severe HIE (5–8). The standard equipment used is a commercially available servo-controlled device (SCD) consisting of either a cooling blanket or cap with a thermostatic mechanism that rapidly cools the neonate to a target rectal temperature of 33.5 ± 0.5°C and maintains it continuously for 72 h (9). At the end of 72 h, the neonate is rewarmed gradually to normothermia over 12 h, as too rapid rewarming can result in worsening of HIE and seizures (10). However, not all NICUs in low- and middle-income countries (LMICs) are equipped with SCD as it is very costly (19750–20000 Euros per set). In recent years, some NICUs in LMICs reported improved survival of moderate and severe HIE neonates following TH using low-cost cooled gel packs (11).

In Malaysia, HIE is common (12). Many Malaysian NICUs started to administer TH on HIE neonates in 2010. To ensure the appropriate use of TH, the Malaysian Ministry of Health (MOH) published a practice guideline (13), which recommended TH to be commenced within 6 h after birth for 72 h on stabilized neonates with moderate or severe HIE and Thompson score (14) ≥7 or seizures. Other criteria which must be met are the presence of at least two of the following: Apgar score <6 at 10 min or needing prolonged resuscitation, presence of acute perinatal events, cord pH of <7 or base deficit of ≥12 mmol/L, or arterial pH < 7.0 or base deficit >12 mmol/L within 60 min of birth. The methods/devices approved for TH were a servo-controlled cooling blanket (SCD-blanket), a servo-controlled cooling cap (SCD-cap), or passive cooling with/without the use of cool gel packs (P±CGPs). SCD was the preferred method, and P±CGP was to be used when SCD was not available. Passive cooling was described as exposing a neonate (without clothing and cap) in a cot to the NICU's air-conditioned ambient temperature (average 22–24°C). If the rectal temperature of the neonate dropped below 33.5°C, the radiant warmer would be used to maintain the rectal temperature at 33–34°C or axillary temperature at 33.5–34.5°C. If the neonate's temperature remained >35°C despite 60 min of passive cooling, cooled gel packs (CGPs) would be used to provide additional cooling. Before use, gel packs (about 4 Euro per pack, bought from local pharmacies) were first cooled with refrigeration without being frozen. They were placed in cotton bags on the neonate under the shoulders or upper back or across the chest.

The Malaysian National Neonatal Registry (MNNR) was established in 2005 and by 2019 had 44 members (comprising all major MOH hospitals, one university hospital, and three private hospitals). Participation in the MNNR was voluntary. Member NICUs prospectively submitted data of neonates using a standardized data form to the MNNR. Since 2012, all LPTNs admitted to these centers and diagnosed to have HIE have been included in the database. Since 2016, information on types of TH administered to each HIE LPTN was also included. This study aimed to investigate the types of therapeutic hypothermia (TH) used and risk factors associated with mortality in these high-risk neonates.

MATERIALS AND METHODS

Study Design

This was an observational retrospective cohort study. The inclusion criteria were all LPTN diagnosed to have HIE and admitted to the NICUs of MNNR between 1 January 2016 and 31 December 2019. The exclusion criteria were gestation of <35 weeks, death in delivery rooms, major malformations, congenital infections, or inborn errors of metabolism. The following data of each recruited neonate was extracted from the MNNR database: demographic characteristics (birth weight, gestation, gender, ethnic group, inborn/outborn, singleton/multiple, mode of delivery), Apgar score at 5 min, admission temperature, highest Thompson score before 6 h of life, HIE severity (mild, moderate, and severe), cooling therapy given (yes, no), type of TH [cooling blanket/cap, passive cooling ± gel packs (P±CGP), both (defined as initially cooled by P±CGP until a set of SCD was available for TH)], late-onset sepsis (LOS) (yes, no), pneumothorax (yes, no), and outcome at discharge (alive or dead). For centers without rectal thermistor probes for monitoring rectal temperature continuously, digital thermometers were used for intermittent measurement of axilla temperature of neonates undergoing TH using P±CGP. During this study, we also conducted a short questionnaire survey of all NICUs on the types and number of sets of TH devices, and methods for monitoring core temperature used during this 4-year period.

Definitions

The following were definitions published annually in a manual provided by the MNNR guiding health care providers in diagnosing and submitting data to the MNNR. Gestation was reported in complete weeks based on antenatal ultrasound, maternal last menstrual period, or the new Ballard score after birth (15). HIE was diagnosed in any neonates with all of the following three criteria: (a) any of three clinical features of encephalopathy within 72 h after birth (abnormal level of consciousness, abnormal muscle tone, abnormal deep tendon reflexes, seizures, abnormal Moro reflex, abnormal sucking reflex, abnormal respiratory pattern, and oculomotor or pupillary abnormalities); (b) three or more findings of acute perinatal events (evidence of fetal distress on antepartum monitoring, cord arterial pH < 7.00, 5-min Apgar score <5, evidence of multi-organ system dysfunction within 72 h of life, abnormal electroencephalogram, and abnormal brain imaging showing ischemia/edema; and (c) absence of underlying congenital cerebral abnormalities/infections or inborn errors of metabolism. The severity of HIE was classified as mild, moderate, or severe according to Sarnat's criteria (16) shortly after birth before 6 h of life. Neonates, who were alert or hyperalert with a normal or exaggerated response to arousal, and no seizures were classified as mild HIE; those with lethargy and decreased response to arousal, with or without a seizure, as moderate HIE; and those in deep stupor or coma at birth and not arousable as severe HIE. LOS was diagnosed in neonates developing symptoms of sepsis after 72 h of life associated with a positive blood culture. The annual incidence of HIE in the MNNR was calculated by dividing the total number of inborn HIE neonates by the total live births in all participating hospitals of the respective years. For this study, NICUs were categorized as small (<50), medium-sized (50–100), and large (>100), based on the number of HIE LPTNs admitted during these 4 years.

Ethics Approval

Parental consent was not obtained as all data were anonymized. Ethical clearance for this study was granted by the Malaysian Ministry of Health and registered under the National Medical Research Registry (NMRR-05-04-168).

Statistical Analysis

Categorical variables were reported as number and percentage, and continuous variables as mean (±SD) or median (range) where appropriate. Demographic, clinical, and outcome data of neonates receiving TH using SCD, P±CGP, or no TH were compared in each category of the severity of HIE. For between-group analysis, the Chi-square test was used for categorical variables, and Student *t*-test for continuous variables, and the Kruskal–Wallis test for among group analysis. Simple and multiple logistic regression analyses were performed to identify significant risk factors associated with in-hospital mortality. The potential risk factors examined were birth weight, gestation, gender, ethnic groups, modes of delivery, inborn/outborn, 5-min Apgar score <5, admission temperature, LOS, pneumothorax, number of HIE neonates admitted per center, types of TH received, the severity of HIE, and Thompson scores. Multicollinearity among independent variables was checked by calculating the variance inflation factor (VIF); variables with a VIF of >3 were removed from the final model. *P*-values of <0.05 were considered statistically significant; all tests were two-sided. Statistical package SPSS v.27 was used for analysis.

RESULTS

Demographic Data

There were 2,761 LPTN with HIE admitted to the 44 NICUs (**Figure 1**); 34.8% of LPTN had mild, 44.6% had moderate, and 20.6% had severe HIE. The majority of neonates in this

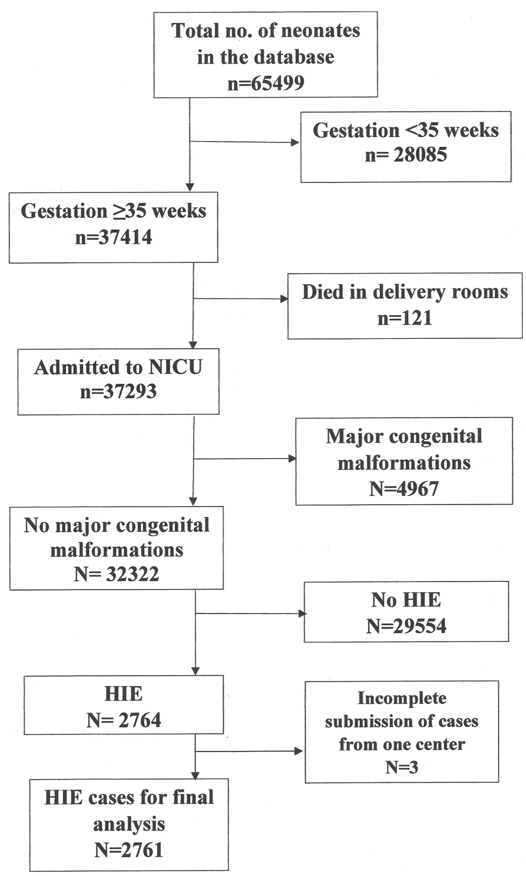

FIGURE 1 | Recruitment flowchart.

cohort were Malays, singletons, and inborn (**Table 1**). The annual incidence of inborn HIE (per 1,000 live births) was 2.2 in 2016, 2.3 in 2017, 2.4 in 2018, and 2.32 in 2019. When compared with inborn HIE neonates, outborns had a lower proportion of mild HIE (20.6% vs. 36.7%), a similar proportion of moderate HIE (46% vs. 44.4%), but a higher proportion of severe HIE (33.4% vs. 18.9%) ($p < 0.001$). A significantly lower proportion of outborns received TH than the inborn (61.3% vs. 66.9%, $p = 0.045$).

Types of Cooling Devices and Therapeutic Hypothermia Rates

All NICUs provided some form of TH to their HIE neonates. Twenty-four (54.5%) NICUs had SCD (**Table 2**). Most (4/5, 80%) large NICUs and smaller NICUs (43.5%) had SCD. Of the total 1,830 (66.3%) neonates receiving TH, 38.5% were by SCD. The most common type of SCD used was cooling blankets (TECOtherm Neo, Tec Com Medizintechnik GMBh, Kabelsketal, Germany, or Artic Sun 5000 Temperature Management System, C.R.Bard, Inc., Louisville, CO, United States). Only one NICU had a set of Cooling Cap (Olympic Cool-Cap cooling system, Natus Medical, Inc., Seattle, WA, United States). The majority of the neonates treated with SCD were admitted to large NICUs. All NICUs monitored rectal temperature during passive TH except in six non-SCD centers.

Figure 2 shows that more HIE neonates were admitted in 2019 than in previous years. The annual TH rates remained static until 2019 when significantly more were cooled using P±CGP (2016: 24.1%, 2017: 26.7%, 2018: 26.9%, 2019: 32.6%; $p = 0.024$), irrespective of HIE severity. There was no significant increase in use of SCD (2016: 39.9%, 2017: 38.3%. 2018: 37.9%, 2019: 38%).

Table 3 shows that the median Thompson scores were higher in the more severe grades of HIE; 39.8% (382/960) of mild, 85% (1,047/1,232) of moderate, and 70.5% (401/569) of severe HIE neonates received TH; and only 51.6% of moderate and 43.6% of severe HIE received TH using SCD.

In-Hospital Mortality

A total of 338 (12.2%) deaths was reported, comprising 1.9% (18/960) of the mild, 4.1% (51/1,232) of the moderate, and 47.3% (269/569) of the severe HIE neonates (**Table 3**). In mild HIE neonates, there was no significant difference in mortality rates irrespective of the types of TH used (no TH: 2.1%, P±CGP: 1.5%, SCD: 1.7%; $p = 0.696$). In moderate HIE neonates, mortality rates were significantly lower with SCD and P±CGP than "no TH"($p < 0.001$). In severe HIE neonates, mortality was significantly lower in those given SCD than with P±CGP ($p = 0.002$) and "no TH" ($p < 0.001$). The most common cause of death reported in each grade of HIE was HIE and not all of them had Thompson score ≥7 (**Table 4**).

Multiple logistic regression analysis shows after controlling for various potential confounders listed in **Table 5**, 5-min Apgar score <5, Cesarean delivery, foreigners, pneumothorax, TH in centers admitted <100 HIE neonates, TH by P±CGP, receiving no TH, moderate or severe HIE, and Thompson scores ≥7 were the significant risk factors associated with mortality. The regression model has a Nagelkerke R square of 0.503, Hosmer and Lemeshow test $p = 0.425$, and Omnibus test of model $p < 0.001$. The area under the receiver operating characteristics curve (ROC) for the predictive model is 0.912 (95% CI: 0.894, 0.930), $p < 0.0001$.

TABLE 1 | Demography and outcome of hypoxic-ischemic encephalopathy (HIE) neonates in the Malaysian National Neonatal Registry (MNNR), 2016–2019.

Variables	HIE stages based on Sarnat criteria			
	Total *N* = 2,761	Mild *N* = 960	Moderate *N* = 1,232	Severe *N* = 569
Thompson score median (IQR)	*N* = 2,755 8 (5,12)	*N* = 958 5 (2, 7)	*N* = 1,229 9 (7, 11)	*N* = 568 13 (10,16)
Gestation, mean (95% CI) weeks	38.6 (38.5, 38.6)	38.6 (38.5, 38.7)	38.7 (38.6, 38.7)	38.5 (38.5, 38.6)
Birth weight, mean (95% CI) g	3, 019 (3, 000, 3, 037)	2, 994 (2, 863, 3, 025)	3, 050 (3, 024, 3, 076)	2, 992 (2, 948, 3, 035)
Males, *n* (%)	1718 (62.2)	609 (63.4)	761 (61.8)	348 (61.2)
Ethnic groups, *n* (%)				
Malay	1791 (64.9)	626 (65.2)	876 (71.1)	289 (50.8)
Chinese	152 (5.5)	60 (6.3)	58 (4.7)	34 (6.0)
Indian	105 (3.8)	46 (4.8)	43 (3.5)	16 (2.8)
Orang Asli	25 (0.9)	7 (0.7)	12 (1.0)	6 (1.1)
Sabah native	211 (7.6)	69 (7.2)	70 (5.7)	72 (12.7)
Sarawak native	90 (3.3)	33 (3.4)	35 (2.8)	22 (3.9)
Other Malaysian	19 (0.7)	5 (0.5)	6 (0.5)	8 (1.4)
Foreigner	368 (13.3)	114 (11.9)	132 (10.7)	122 (21.4)
Singleton, *n* (%)	2707 (98.1)	940 (98.0)	1212 (98.4)	555 (97.5)
Inborn, *n* (%)	2435 (88.2)	893 (93.0)	1082 (87.8)	460 (80.8)
In-hospital mortality, *n* (%)	338 (12.2)	18 (1.9)	51 (4.1)	269 (47.3)
Median duration of hospitalization of all neonates, in days (IQR)	8 (5, 13)	6 (5, 10)	9 (6, 14)	9 (3, 19)

CI, confidence intervals; HIE, hypoxic-ischemic encephalopathy; IQR, interquartile range.

TABLE 2 | Frequency distribution of cooling devices and number of neonates with hypoxic ischemic encephalopathy in different types of neonatal intensive care units (NICUs), 2016–2019.

Variables	Small NICU	Medium sized NICU	Large NICU	Overall
No. of NICUs	23	16	5	44
Total no. of HIE neonates admitted (%) during the 4 years	689(25.0)	1, 057(38.3)	1, 015(36.8)	2,761 (100)
No. of HIE neonates admitted per NICU, median (range) during the 4 years	36(1 – 49)	64.5(51 – 95)	128(106 – 436)	49 (1-436)
No. of NICU with different types of TH devices (%)				
Had SCD only	8 (34.8)	6 (37.5)	2 (40)	16 (36.4)
Had gel packs only	8 (34.8)	3 (18.8)	1 (20)	12 (27.3)
Had both SCD and gel packs	2 (8.7)	4 (25.0)	2 (40)	8 (18.2)
Had no devices	5 (21.7)	3 (18.8)	0 (0)	8 (18.2)
No. of NICUs with SCD per NICUs (%)				
0 set	13 (56.5)	6 (37.5)	1 (20)	20 (45.5)
1 set	8 (34.8)	7 (43.8)	0	15 (34.1)
2 sets	2 (8.7)	3 (18.8)	4 (80)	9 (20.5)
No. of neonates treated with				
SCD only (%)	115 (16.7)	335 (31.7)	613 (60.4)	1063 (38.5)
P±CGP only (%)	290 (42.1)	300 (28.4)	80 (7.9)	670 (24.3)
Both methods (%)	44 (6.4)	43 (4.1)	10 (1.0)	97 (3.5)
No treatment (%)	240 (34.8)	379 (35.9)	312 (30.7)	931 (33.7)

NICU, neonatal intensive care units; HIE, hypoxic-ischemic encephalopathy; TH, therapeutic hypothermia; SCD, servo-controlled device.

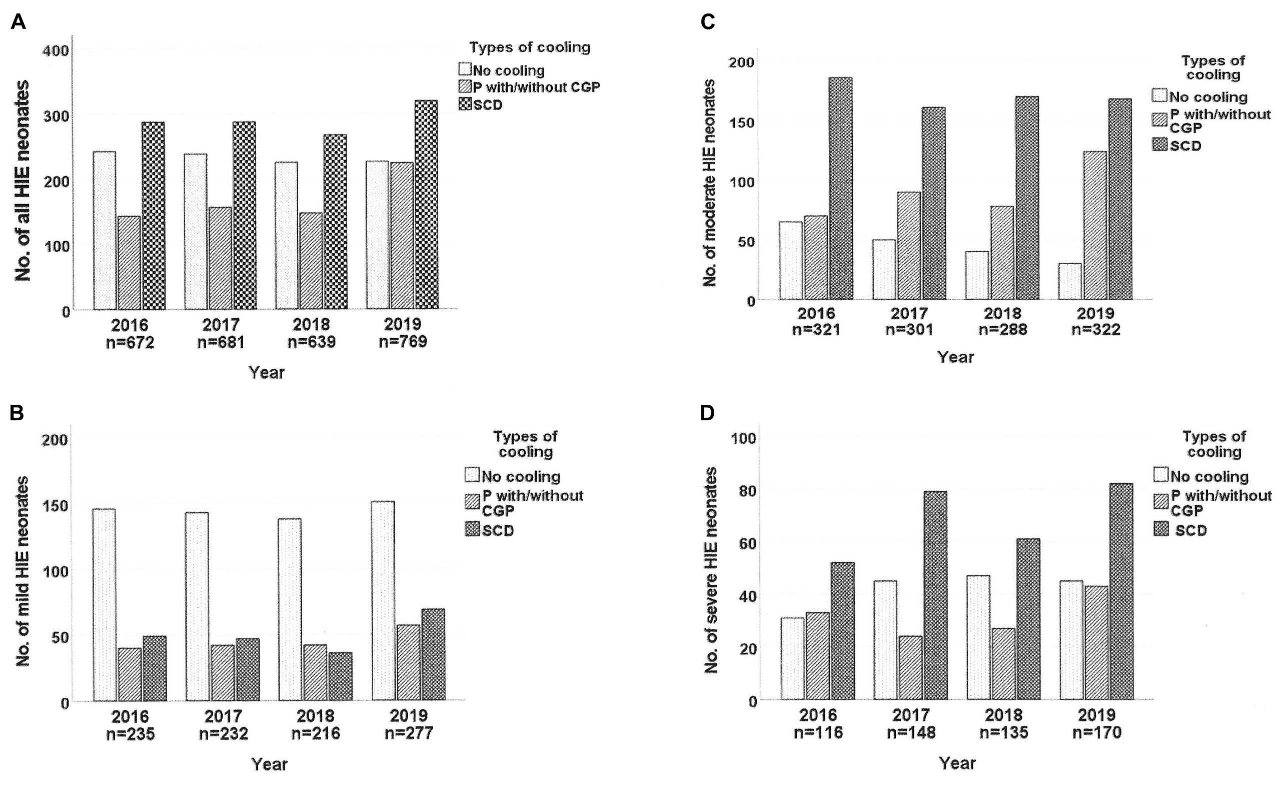

FIGURE 2 | Trends of therapeutic hypothermia used for neonates with hypoxic-ischemic encephalopathy in the MNNR between 2016 and 2019. HIE, hypoxic-ischemic encephalopathy; P with/without CGP, passive cooling with/without uses of cooled gel packs; SCD, servo-controlled devices.

DISCUSSION

In this observational retrospective cohort study of HIE neonates in the MNNR, we found that all Malaysian NICUs provided some form of TH using either SCD or P±CGP, as only 55.4% of our NICUs had SCD. TH using SCD was received by 18.6% of mild, 51.6% of moderate, and 43.6% of severe HIE neonates. Multiple logistic regression analysis identified several factors to

TABLE 3 | Comparison of demographic, clinical and outcome characteristics of neonates with mild, moderate, and severe HIE (based on Sarnat Criteria) treated with different types of therapeutic hypothermia.

Variables	Mild HIE *N* = 960			Moderate HIE *N* = 1232			Severe HIE *N* = 569		
	No TH *N* = 578	[a]P±CGP *N* = 203	SCD *N* = 179	No TH *N* = 185	[b]P±CGP 411	SCD *N* = 636	No TH *N* = 168	[c]P±CGP *N* = 153	SCD *N* = 248
Thompson scores median (IQR)	*N* = 577 4 (2, 6)	6 (4, 8)	*N* = 178 7 (5, 9)†	9 (7, 11)	9 (7, 11)	*N* = 633 9 (7, 12)§§	14 (10, 16)	*N* = 152 13 (10, 17)	13 (9 – 16)
Birth weight, g, mean (SD)	2, 994 (494)	2, 996 (481)	2,992 (494)	3, 041 (472)	3, 017 (447)	3, 074 (487)	2, 923 (512)	2, 984 (507)	3, 042 (542)
Gestation, weeks, median (IQR)	39 (38, 40)	39 (37, 40)	39 (38, 39)	39 (38, 40)	39 (38, 40)	39 (38, 40)	39 (37, 40)	39 (38, 40)	39 (38, 40)
Males, *n* (%)	363 (62.8)	126 (62.1)	120 (67.0)	113 (61.1)	230 (56.0)	418 (65.7)	88 (52.4)	98 (64.1)	162 (65.3)
Ethnic groups, *n* (%)									
Malay Malaysian	367 (63.5)	142 (70.0)	117 (65.4)	122 (65.9)	283 (68.9)	471 (74.1)	98 (58.3)	82 (53.6)	109 (44.0)
Other Malaysian	138 (23.9)	42 (20.7)	40 (22.3)	42 (22.7)	79 (19.2)	103 (16.2)	42 (25.0)	37 (24.2)	79 (31.9)
Foreigner	73 (12.6)	19 (9.4)	22 (12.3)	21 (11.4)	49 (11.9)	62 (9.7)	28 (16.7)	34 (22.2)	60 (24.2)**
LSCS, *n* (%)	194 (33.6)	68 (33.5)	49 (27.4)	73 (39.5)	123 (29.9)	160 (25.2)§	82 (48.8)	71 (46.4)	111 (44.8)
Outborns, *n* (%)	45 (7.8)	14 (6.9)	8 (4.5)	38 (20.5)	33 (8.0)	79 (12.4)§	43 (25.6)	25 (16.3)	41 (16.5)**
5-min Apgar score, median (IQR)	6 (5, 8)	6 (4, 7)	6 (5, 7)†	*N* = 182 6 (4,7.3)	*N* = 402 5 (4, 6)	*N* = 629 5 (4, 6)§	*N* = 152 3 (1, 5)	*N* = 148 4 (2,5)	*N* = 227 4 (2, 5)
Type of NICU, *n* (%)									
Small	164 (28.4)	102 (50.2)	32 (17.9)†	36 (19.5)	162 (39.4)	53 (8.3)	40 (23.8)	70 (45.8)	30 (12.1)
Medium size	255 (44.1)	79 (38.9)	56 (31.3)	67 (36.2)	205 (49.9)	186 (29.2)	57 (33.9)	59 (38.6)	93 (37.5)
Large	159 (27.5)	22 (10.8)	91 (50.8)	82 (44.3)	44 (10.7)	397 (62.4)§	71 (42.3)	24 (15.7)	125 (50.4)*
Admission temperature, median (IQR) °C	36.4 (35.8, 36.7)	36.1 (35.5, 36.6)	36.0 (35.0, 36.5)†	36.0 (35.1, 36.5)	36.0 (34.6, 36.5)	35.6§ (34.5, 36.4)	35.5 (34.2, 36.3)	35.4 (34.0, 36.4)	35.3 (34.3, 36.1)
LOS, *n* (%)	4 (0.7)	0	2 (1.1)	2 (1.1)	3 (0.7)	6 (0.9)	5 (3.0)	3 (2.0)	3 (1.2)
Pneumothorax, *n* (%)	29 (5.0)	7 (3.4)	11 (6.1)	15 (8.1)	21 (5.1)	23 (3.6)§§	13 (7.7)	13 (8.5)	15 (6.0)
Died, *n* (%)	12 (2.1)	3 (1.5)	3 (1.7)	22 (11.9)	16 (3.9)	13 (2.0)§	117 (69.6)	74 (48.4)	78 (31.5)*
Age of death, median (IQR) days	15 (1.0, 13.3)	1 (1, 1)	2 (1, 2)	2 (1, 5.3)	2 (1, 2)	5 (2.5, 19.0)§§	1 (1, 4)	3 (2, 8)	4 (2, 7.3)*
Duration of hospital stay of survivors, median (IQR) days	6 (4, 9)	7 (6, 11)	8 (6, 11)†	11 (8, 17)	10 (7, 14)	9 (6, 14)§	23 (12, 36)	21 (13, 28)	15 (9, 22)*

*HIE, hypoxic-ischemic encephalopathy; TH, therapeutic hypothermia; SCD, servo-control device; P±CGP, passive cooling with/without cool gel pack; LSCS, lower segment Cesarean section; LOS, late-onset sepsis; SD, standard deviation; IQR, interquartile range. The P±CGP groups in this table also included those neonates cooled with both methods: [a]n = 22; [b]n = 46; [c]n = 44. Comparison of variables among neonates receiving different types of TH in each category of HIE: Severe HIE, *p < 0.001, **p < 0.05; Moderate HIE, §p < 0.001, §§p < 0.05; Mild HIE: †P < 0.001.*

TABLE 4 | Causes of death of hypoxic-ischemic encephalopathy according to the severity.

Causes of death	Mild HIE *N* = 18 (%)		Moderate HIE *N* = 51 (%)		Severe HIE *N* = 269 (%)		All HIE *N* = 338 (%)
	Death	Thompson score ≥7	Death	Thompson score ≥7	Death	Thompson score ≥7	
HIE	8 (44.4)	4	27 (52.9)	23	251 (93.3)	241	286 (84.6)
MAS	3 (16.7)	1	7 (13.7)	6	0	0	10 (3.0)
PPHN	0	0	2 (3.9)	2	0	0	2 (0.6)
Sepsis	0	0	6 (11.7)	5	3 (1.1)	3	9 (2.7)
Pneumonia	1 (5.6)	1	3 (5.9)	3	1 (0.4)	1	5 (1.5)
Pneumothorax	0	0	1 (2.0)	1	0	0	1 (0.3)
NEC perforated	1 (5.6)	0	0	0	0	0	1 (0.3)
IVH	1 (5.6)	0	0	0	0	0	1 (0.3)
Twin-twin transfusion	0	0	1 (2.0)	0	0	0	1 (0.3)
Myopathy	0	0	1 (2.0)	1	0	0	1 (0.3)
Not stated	4 (22.2)	3	3 (5.9)	2	14 (5.2)	12	21 (6.2)

HIE, hypoxic-ischemic encephalopathy; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage.

be significantly associated with mortality, including the severity of HIE, no TH, and TH using P±CGP.

Presently, the most reliable methods to diagnose and grade HIE are magnetic resonance imaging (MRI) and electroencephalogram (EEG). However, the majority of the Malaysian NICUs did not have timely access to MRI services during the study period, and only 22/44 NICUs had amplitude-integrated EEG (aEEG). The Sarnat score and Thompson scores were (and still are) used for diagnosis and management of HIE by the managing neonatologists in our NICUs. The findings in the present study suggested that both the Sarnat score and Thompson score could have misclassified some of the neonates, as we found some mild HIE neonates had high Thompson scores of ≥7 and died due to HIE (**Table 4**); and some moderate and severe HIE neonates who died due to HIE had low Thompson scores.

Many of the HIE neonates were treated with P±CGP in our NICUs. Although this resourceful method was commendable, multiple logistic regression analysis in our study showed that, after controlling for various potential confounders, its use was associated with a significantly higher (>1.5 times) risk of mortality than SCD. The major problems of using P±CGP include difficulty in maintaining a constant core temperature and labor-intensiveness. A neonate on P±CGP needs a longer time to achieve the target core temperature (about 1 h). Each gel packs in-use needs to be changed every 3–4 h to maintain the target temperature. Some NICUs used axillary temperature as a surrogate for monitoring core temperature which could further compromise the effectiveness of P±CGP, as the axillary temperature does not reflect core temperature accurately.

According to current management guidelines (8, 13), TH was indicated only for neonates with moderate and severe HIE. In this cohort, there were 18.6% of mild HIE neonates treated with TH using SCD. The benefits of TH in mild HIE are still controversial and side effects have been reported (17, 18). Yet, at the same time, there were 353 (19.6%) moderate or severe HIE neonates receiving no TH. It is uncertain whether this was due to their failure to meet the criteria for TH, or the ignorance of some staff on the benefits of TH. The significant increase in TH during the fourth year (2019) suggested that perhaps more NICU staff were aware of these benefits recently. However, because of the inadequate number of SCD, this increasing trend of TH was reflected mainly by increased use of P±CGP.

During the study period, there were only five large NICUs; they had more sets of SCD per NICU than many smaller NICUs and treated more neonates with SCD and had lower mortality rates. Their better outcome could be attributed to be having overall better equipment and expertise than many smaller NICUs. These findings suggest that the regionalization of TH in Malaysia may lead to better outcomes for HIE neonates in this country. However, for TH to be effective, it must be administered within the first 6 h of life (5, 6, 8). Like many LMICs, traffic jams and/or inadequate neonatal transportation services in Malaysia are common barriers to ensure high-risk outborns reaching regional NICUs for TH within 6 h of birth. A second option to improve outcomes is to equip all Malaysian NICUs with an adequate number of sets of SCD to provide effective TH equitably and timely to any neonate who needs it.

Currently, all NICUs provided care to all grades of HIE. Our findings suggest that to improve outcomes of HIE neonates in Malaysia, equipping NICUs with adequate sets of SCD, supportive equipment, and trained personnel, and improving access to diagnostic facilities for HIE should be considered.

Our real-world findings concur with those reported from HICs that TH was associated with better survival in both moderate and severe HIE neonates (8). Our results contrasted with those of a multicenter randomized controlled study (the HELIX study) carried out in several NICUs in three LMICs, which reported significantly higher mortality associated with TH than no TH (19). Besides the difference in the design of their study, other possible reasons for the differences in the outcome of TH between the present study and the HELIX study include the relatively smaller sample size, different diagnostic criteria used, and a much higher proportion (80%) of outborn neonates recruited in the HELIX study.

TABLE 5 | Simple and multiple logistic regression analyses of potential risk factors associated with in-hospital mortality in all HIE neonates in the Malaysian National Neonatal Registry (MNNR), 2016–2019.

Variables	In-hospital mortality *N* = 338	Alive *N* = 2423	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Birth weight, mean (SD) g	2,953 (533)	3,027 (484)	1.000 (0.999, 1.000)	1.000 (1.000,1.000)
Gestation, mean (SD) weeks	38.4 (1.6)	38.6 (1.4)	0.883 (0.816, 0.955)	0.969 (0.862, 1.089)
Gender				
Females	141	902	1	1
Males	197	1521	0.829 (0.657, 1.044)	1.043 (0.759, 1.433)
Ethnic groups				
Non-Malay Malaysians	71	531	1	1
Malay Malaysians	194	1597	0.909 (0.680, 1.213)	1.222 (0.831, 1.798)
Foreigners	73	295	1.851 (1.296, 2.643)	1.646 (1.006, 2.692)
Modes of delivery				
Vaginal route	151	1679	1	1
Cesarean section	187	744	2.795 (2.218, 3.522)	2.335 (1.700, 3.207)
Birthplace				
Inborn	276	2159	1	1
Outborn	62	264	1.837 (1.356, 2.489)	1.063 (0.665, 1.700)
5-min Apgar score				
5–10	102	1610	1	1
<5	213	757	4.441 (3.454, 5.710)	1.436 (1.019, 2.023)
Missing data	23	56	–	
Admission temperature, *n*				
>36.6	51	564	1	1
35.0–36.5	160	1314	1.347 (0.968, 1.874)	0.899 (0.579, 1.394)
33.0-<35.0	101	491	2.275 (1.591, 3.253)	1.184 (0.722, 1.944)
<33.0	26	54	5.325 (3.076, 9.216)	1.1143 (0.538, 2.427)
Late-onset sepsis				
No	328	2405	1	1
Yes	10	18	4.074 (1.864, 8.900)	2.889 (0.879, 9.496)
Pneumothorax				
No	296	2318	1	1
Yes	42	105	3.132 (2.147, 4.570)	3.435 (1.996, 5.914)
No. of HIE cases admitted				
≥100	98	917	1	1
50-<100	142	915	1.452 (1.105, 1.908)	1.552 (1.065, 2.260)
<50	98	591	1.552 (1.151, 2.091)	1.898 (1.225, 2.940)
Type of Therapeutic hypothermia				
Servo-control devices	109	1051	1	1
Passive cooling ± gel packs	78	592	1.270 (0.934, 1.728)	1.553 (1.031, 2.338)
No TH	151	780	1.867 (1.435, 2.429)	4.749 (3.201, 7.045)
Severity of HIE, *n*				
Mild	18	942	1	1
Moderate	51	1181	2.260 (1.312, 3.894)	2.823 (1.495, 5.333)
Severe	269	300	46.926 (28.62, 76.95)	34.925 (18.478, 66.012)
Thompson scores				
<7	29	844	1	1
7–13	132	1309	2.935 (1.945, 4.427)	1.776 (1.023, 3.082)
≥14	176	265	19.329 (12.747, 29.311)	3.641 (2.000, 6.629)
Missing data	1	5	–	

(Continued)

TABLE 5 | (Continued)

HIE, hypoxic-ischemic encephalopathy; SD, standard deviation; CI, confidence intervals; TH, therapeutic hypothermia.

Many studies from HICs reported better long-term neurodevelopmental outcomes and cost-effectiveness in survivors of moderate HIE following TH (20, 21). In Malaysia, there is a need to carry out similar studies to confirm the benefits of TH on these high-risk neonates, including comparing the outcome of HIE neonates treated with P±CGP vs. SCD, like studies reported in other LMICs (11, 22).

The strengths of this study include its large sample size, inclusion of all HIE neonates from all the major NICUs in a middle-income country, systematic and prospective collection of patients using a standard format, and comparison of mortality of HIE receiving different types of TH in a real-world situation. The major limitations of this study are not a randomized controlled study; no information included in the MNNR database on each neonate's Apgar score at 10 min, mechanical ventilation or resuscitation at 10 min, cord pH, and clinical features of HIE for us to verify the diagnostic accuracy of HIE in this study; no information in the database on the timing of Sarnat examination, seizures prevalence during the first 6 h of life, actual age, and indications for commencement of TH, age of initiation and duration of TH, adverse effects of TH, brain MRI findings, and neurological findings at discharge.

CONCLUSION

Both SCD and P±CGP were used for TH in Malaysian NICUs. Moderate/severe HIE, TH using P±CGP, and receiving no TH were among the risk factors associated with mortality.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Medical Research Registry of the Ministry of Health of Malaysia. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the National Legislation and the Institutional Requirements.

AUTHOR CONTRIBUTIONS

NB: conceptualization, data analysis, and manuscript preparation. NB, SN, and SC: data extraction and review and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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Level of Postnatal Checkup in Ethiopia – Implications for Child Health Services

Binyam Minuye Birhane[1]*, Wubet Alebachew Bayih[1], Demewoz Kefale Mekonen[1], Ermias Sisay Chanie[1], Solomon Demis[1], Habtamu Shimelis[1], Worku Necho Asferie[1], Eskeziaw Abebe[2], Dagne Addisu[1], Gedefaye Nibret[1], Aklilu Endalamaw[3,4], Tigabu Munye[1], Desalegn Abebaw Jember[5], Samuel Nebiyu[6], Yenework Mulu Tiruneh[7] and Demeke Mesfin Belay[1]

[1] College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia, [2] College of Health Sciences, Woldia University, Woldia, Ethiopia, [3] School of Public Health, The University of Queensland, Brisbane, QLD, Australia, [4] School of Health Sciences, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia, [5] St. Paul's Hospital, Addis Ababa, Ethiopia, [6] College of Medicine and Health Sciences, Wollo University, Dessie, Ethiopia, [7] College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

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Andrew Steenhoff,
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Ministry of Health, Malaysia
Henna Shaikh,
Children's Hospital of Philadelphia,
United States

***Correspondence:**
Binyam Minuye Birhane
biniamminuye@yahoo.com

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Background: High neonatal mortality rates continue to be a major public health issue in Ethiopia. Despite different maternal and neonatal care interventions, neonatal mortality in Ethiopia is at a steady state. This could be due to the low utilization of neonatal checkups. Thus, nationally assessing the level and predictors of postnatal checkups could provide important information for further improving neonatal healthcare services.

Materials and Methods: A secondary data analysis of the 2016 Ethiopia Demographic and Health Survey (EDHS) was performed on 7,586 women who had live births in the 2 years before the survey. All variables with a p-value of $\leq$0.25 in the bivariable analysis were entered into the final model for multivariable analysis, and the level of statistical significance was declared at a P-value of $<$0.05.

Results: According to the national survey, only 8.3% [95% CI: 8.19, 8.41] of neonates received postnatal checkups. About two-thirds of women, 62.8% had antenatal care visits, 67.9%, gave birth at home, and 95.7% were unaware of neonatal danger signs. Distance from health care institutions [AOR = 1.42; 95% CI: 1.06, 1.89], giving birth in a healthcare facility [AOR = 1.55; 95% CI: 1.12, 2.15], antenatal care visit [AOR = 3.0; 95% CI: 1.99, 4.53], and neonatal danger signs awareness [AOR = 3.06; 95% CI: 2.09, 4.5] were all associated with postnatal care visits.

Conclusion: The number of neonates who had a postnatal checkup was low. Increasing antenatal care visit utilization, improving institutional delivery, raising awareness about neonatal danger signs, increasing access to health care facilities, and implementing home-based neonatal care visits by healthcare providers could all help to improve postnatal checkups.

Keywords: EDHS, Ethiopia, neonatal checkup, postnatal visit, neonate

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Abbreviations: AOR, adjusted odd ratio; ANC, antenatal care visit; CI, confidence interval; DHS, Demographic and Health Survey; EDHS, Ethiopian Demographic and Health Survey; PNC, postnatal care visit; SDG, sustainable development goal; WHO, World Health Organization.

INTRODUCTION

The postnatal period is defined as the period from 1 h after delivery of the placenta until 6 weeks postpartum. This period marks the establishment of a new phase of family life for women and their partners and the beginning of lifelong health for the newborns (1). Most neonatal deaths occur during this critical period in the lives of mothers and newborns (2).

In 2019, 2.4 million neonates died in their first month of life worldwide, with approximately 7,000 newborns dying every day. Despite a decrease in neonatal deaths from 5 million in 1990 to 2.4 million in 2019, the burden in Sub-Saharan Africa and Southern Asia remains high (3). Ethiopia, with 30 deaths per 1,000 live births, is one of the Sub-Saharan African countries with a high burden of neonatal mortality. Prematurity (21.8%), birth asphyxia (31.6%), and sepsis (18.5%) are the leading causes of neonatal deaths in Ethiopia (4).

The World Health Organization (WHO) proposed that by 2035, all countries will have achieved the goal of 10 or fewer newborn deaths per 1,000 live births and that they will continue to reduce death and disability, ensuring that no newborn is left behind. Improved skilled birth attendants, antenatal care visits, and neonatal care coverage, including home-based newborn care, could help achieve this goal. In addition, another WHO strategic objective to achieve reduced neonatal mortality is to leverage the power of parents, families, and communities (5).

Furthermore, all babies, regardless of birthplace, should receive neonatal care within the first 24 h of life, should be discharged from the birthing facility no sooner than 24 h after birth, and should receive at least four checkups within the first 6 weeks of life. Neonatal checkups are one of the milestones in the continuum of care required to achieve optimal maternal and child health. Neonatal care should be provided from a woman-friendly perspective. WHO emphasizes the importance of early post-hospital discharge follow-up by an experienced clinician for both women and their families (6) with the involvement of health workforce support, a woman-friendly perspective, and adequate infrastructure (7). As a result, psychosocial postpartum support programs have been promoted to improve maternal knowledge, attitudes, and skills related to parenting, maternal mental health, maternal quality of life, maternal physical health, timely recognition of danger signs, financial availability to arrange for transportation, affordability of health care costs, and accessibility to a health facility (8, 9).

Evidence shows that poor healthcare-seeking behaviors for neonatal illness, poorly perceived seriousness of the illness, cultural malpractices, and poor socioeconomic status are some of the barriers to utilization of neonatal care visits (10). Furthermore, delays in seeking healthcare, a lack of women's autonomy to seek care, a lack of money, a heavy workload at home, deeply rooted cultural beliefs and rituals that guide care-seeking behavior, and restrictions on new mothers' and newborns' mobility for care-seeking all contribute to the problem (11, 12). Furthermore, the low coverage and poor quality of neonatal care provided reflect a persistently neglected component of maternity services and a gap in the continuum of neonatal care visit utilization (13). As a result, timely neonatal care visits and community-based intervention strategies, such as home visiting, health education, and counseling, are recommended (14, 15).

Maternal and child health care coverage is low in Ethiopia. Among pregnant women, an estimated 62% receive ANC and the rate of delivery in a health facility is 27%. The proportion of women receiving a postnatal check-up within 2 days of delivery is higher in urban areas (48%) than in rural areas (29%), lowest in Somalia (10%), and highest (74%) in Addis Ababa (16). Studies conducted in Ethiopia to identify the magnitude and determinants of postnatal care visits for neonates have inconsistent and inconclusive findings (17–22). ANC visit, place of delivery, residence, distance from the healthcare facility, educational status, age of the respondents, and mode of delivery were some of the factors that affect the postnatal checkup (17, 22–24). Therefore, this study helps estimate the overall rate of neonatal checkups and the factors associated with completing neonatal checkups in Ethiopia.

MATERIALS AND METHODS

Data Source and Sampling Design

The data was taken from the 2016 EDHS report, which was conducted from January 18 to June 27, 2016. In Ethiopia, there are nine regional states and two city administrations. Each region was stratified into urban and rural areas. Stratified two-stage cluster sampling was performed. Samples of enumeration areas (EAs) were selected independently in each stratum in two stages. A total of 645 EAs (202 in urban areas and 443 in rural areas) were selected with a probability proportional to EA size. The full details are available from reference 16 (16).

Lists of households were used as a sampling frame for the second stage of household selection, and a fixed number of 28 households per cluster were chosen with an equal probability of systematic selection from the newly created household listing. The study population consisted of women with postpartum with a baby in the selected enumeration areas (EAs) and all postpartum mothers who had neonates in Ethiopia (16).

The data was extracted from 7,586 women with postpartum. The approval letter was obtained from the measure demographic and health survey (DHS), and the data set was downloaded from the DHS website[1].

Inclusion Criteria

All women with postpartum aged 15–49, who were either permanent residents or visitors who stayed in the selected households the night before the survey, were eligible.

Dependent variable: The primary outcome of interest was postnatal checkups for neonates (PNC). This variable was dummy-coded, so respondents who reported having PNC checkups for neonates were coded as "Yes," while those who did not have PNC checkups were coded as "No."

A postnatal care visit for a neonate was defined as at least one PNC visit within the first 42 days of the neonate's postpartum period (25).

[1] http://www.dhs.com

Exposure Variables

Socio-demographic variables: Age of the mother's residence (urban or rural), religion, marital status, and educational status (no education, primary education, secondary education, and above education).

Antenatal care visit (ANC) is defined based on self-reported frequency of any ANC services provided by skilled healthcare providers in the healthcare institutions, and categorized as "Yes" for any ANC visit and "No" for no ANC visit.

Place of delivery: Refers to whether the delivery was at a healthcare institution or home.

Fertility-related factors include the most recent child's birth order (1st, 2nd, 3rd, 4th, etc.).

Mode of delivery: How did you give birth (vaginally, C/S, or instrumentally)?

Facility-related variables include the mother's perceived distance from home to a health facility categorized as a "big problem" or "not a big problem."

Statistical Analysis

Data cleaning, recording, and analysis were carried out using SPSS statistical software version 24. Sample weight was applied to all analysis procedures to account for complex survey design and unequal probabilities of selection. A Rao-Scott chi-square test that adjusts for complex sample design was used to examine the bivariate associations between each covariate and the outcome variable. The data was a national survey data set with a hierarchical and cluster nature, which emphasizes the need for us to use a multilevel model of analysis. To use this model, the interclass calculation should be calculated, and be greater than 10%. The ICC in the current study was found to be 8.9%, which is lower than expected. As such, we used the binary logistic regression model. All variables with a p-value of ≤ 0.25 in the bivariable analysis were entered into the final model for multivariable analysis, and variables with p-values of < 0.05 in the multivariable binary logistic regression model analysis were considered statistically significant. Finally, the result was presented using frequencies, tables, and texts.

RESULTS

Socio-Demographic and Economic Characteristics of Mothers

The current EDHS analysis included 7,586 women who had a live birth in the 2 years preceding the survey. Almost half of the women (50.4%) were between the ages of 25 and 34, and 93.7% were married. The vast majority, 87.2%, came from rural areas. Seventy-eight percent of women were orthodox, while 37.2% were Muslim. Almost two-thirds of women, or 63.1%, were illiterate (**Table 1**).

Characteristics of Mothers and Neonatal Visit

More than half of women (58.1%) perceived the distance from nearby health facilities as a major problem for utilization of PNC checkups. Regarding ANC visits, 62.8% of women had antenatal care visits, and more than two-thirds (67.9%) of women gave birth at home. The majority (97.6%) of women gave birth vaginally and 95.7% had no awareness of danger signs (**Table 2**).

TABLE 1 | Socio-demographic characteristics of women with postpartum in Ethiopia (N = 7,586).

Variables	Frequency	Percentage (%)
Age		
15–24 years	1,804	23.8
25–34 years	3,823	50.4
>35 years	1,959	25.8
Residence		
Urban	969	12.8
Rural	6,617	87.2
Marital status		
Unmarried	481	6.3
Married	7,105	93.7
Religion		
Orthodox	2,881	38.0
Muslim	2,821	37.2
Protestant	1,651	21.8
Others	233	3.0
Educational status		
No education	4,788	63.1
Primary education	2,149	28.3
Secondary and above	649	8.6
Wealth index		
Poorest	1,649	21.7
Poorer	1,654	21.8
Middle	1,588	20.9
Richer	1,427	18.9
Richest	1,268	16.7

The Magnitude of Postnatal Checkup

Six hundred thirty-two women, or 8.3%, had PNC for neonates within 42 days of giving birth.

Determinants of Postnatal Checkup for Neonate

Binary logistic regression, in both bivariable and multivariable forms, was attempted. In a bivariable binary logistic regression analysis, residence, educational status, antenatal care visit, place of delivery, mode of delivery, awareness of neonatal danger signs, perceived distance from the health facility, and birth order were all the significant factors associated with postnatal checkups. The place of birth, ANC visit, and awareness of neonatal danger signs were all statistically significant predictors of postnatal checkups in the multivariable binary logistic regression analysis (**Table 3**).

Women who perceived distance from healthcare institutions as not being a major issue were 1.42 times more likely than women who perceived distance as a major issue [AOR = 1.42; 95% CI: 1.06, 1.89]. Women who gave birth in a healthcare facility were 1.55 times more likely than women who gave birth at home to have postnatal care visits [AOR = 1.55;

TABLE 2 | Characteristics of the study sample and postnatal checkup for neonates (PNC) in Ethiopia (*N* = 7,586).

Variables	Total	PNC checkup		*P*-value*
	Frequency (%)	Yes	No	
Residence				<0.001
Urban	969 (12.8)	177 (18.3)	792 (81.7)	
Rural	6,617 (82.2)	455 (6.9)	6,162 (93.1)	
Educational status				<0.001
No education	4,788 (63.1)	315 (6.6)	4,473 (93.4)	
Primary education	2,149 (28.3)	198 (9.2)	1,951 (90.8)	
secondary and above	649 (8.6)	119 (18.4)	530 (81.6)	
Distance to health facility				<0.001
Big problem	4,404 (58.0)	249 (5.7)	4,154 (94.3)	
Not big problem	3,182 (42.0)	383 (12.0)	2,800 (88.0)	
ANC visit				<0.001
Yes	4,753 (62.8)	553 (11.6)	4,200 (88.4)	
No	2,818 (37.2)	79 (2.8)	2,739 (97.2)	
Mode of delivery				<0.001
Cesarean section	183 (2.4)	587 (7.9)	6,816 (92.1)	
Vaginal	7,403 (97.6)	45 (24.8)	138 (75.2)	
Awareness on neonatal danger sign				<0.001
Yes	330 (4.3)	107 (32.4)	223 (67.6)	
No	7,256 (95.7)	526 (7.2)	6,731 (92.8)	
Place of birth				<0.001
Health institution	2,401 (32.1)	363 (15.1)	2,038 (84.9)	
Home	5,071 (67.9)	252 (5.0)	4,819 (95.0)	
Birth order				0.002
1st	1,435 (18.9)	163 (11.4)	1,272 (88.6)	
2–4	3,188 (42.0)	265 (8.3)	2,923 (91.7)	
≥5	2,963 (39.1)	204 (6.9)	2,759 (93.1)	

**Rao-Scott chi-square p-value.*

TABLE 3 | Determinants of PNC visit for neonates among women with postpartum in Ethiopia.

	Postnatal visit (Yes, No)	
	Crude odd ratio	Adjusted odd ratio
Residence		
Urban	3.03 (2.20, 4.18)	1.39 (0.91, 2.08)
Rural	1	1
Educational status		
No education	1	1
Primary education	1.43 (1.10,1.90)	0.87 (0.63,1.19)
Secondary and above	3.2 (2.30, 4.39)	1.0 (0.62,1.60)
Distance to health facility		
Big problem	1	1
Not big problem	2.28 (1.78, 2.91)	1.42 (1.06, 1.89)**
ANC visit		
Yes	4.60 (3.19, 6.57)	3.0 (1.99, 4.53)**
No	1	1
Place of birth		
Health institution	3.38 (2.60, 4.39)	1.55 (1.12, 2.15)*
Home	1	1
Mode of delivery		
Cesarean section	3.85 (2.29, 6.41)	0.98 (0.48, 2.03)
Vaginal	1	1
Awareness of neonatal danger signs		
Yes	6.13 (4.28, 8.77)	3.06 (2.09, 4.5)**
No	1	1
Birth order		
1st	1.73 (1.28, 2.35)	1.03 (0.69, 1.54)
2–4	1.23 (0.93,1.62)	0.88 (0.64,1.23)
≥5	1	1

**p-value < 0.009, **p-value < 0.001.*

95% CI: 1.12, 2.15]. Furthermore, women who had ANC visits were three times more likely to use neonatal care visits than women who did not have ANC visits [AOR = 3; 95% CI: 1.99, 4.53]. Women who were aware of neonatal danger signs were three times more likely to seek neonatal care than women who were unaware [AOR = 3.06; 95% CI: 2.09, 4.5] (**Table 3**).

DISCUSSION

Postnatal care visits are essential for increasing neonatal survival. This study aimed to determine the proportion of PNC and factors associated with PNC among women with postpartum in Ethiopia. We found that the postnatal checkup rate was 8.3%. The magnitude of PNC visits in the current study is lower than findings from Morocco (30.1%) (26), Nigeria (28.9%) (27), Ghana (62%) (28), India (29%) (29), and Nepal (43.2%) (30). One possible reason could be that the current study only included PNC, whereas other studies included postnatal checkups for mothers and neonates, which affects the overall magnitude of the postnatal care visit. Furthermore, it could be due to differences in the study setting, data collection method, and target population.

Women who perceived their distance from healthcare institutions as not being a major issue were 1.42 times more likely to use the neonatal care checkup than women who perceived distance from healthcare institutions as being a major issue. The finding is similar to studies conducted in Indonesia (31) and developing countries (32). This could be because women who live a long distance away from a healthcare facility may have difficulty obtaining transportation (33, 34). Furthermore, it causes a maternal delay in seeking healthcare services (35).

Women who had ANC visits were three times more likely than women who did not have ANC visits to use a PNC checkup. The finding is supported by studies conducted in Ethiopia (22, 27, 28, 30, 36, 37). Previous studies suggest that antenatal care visits increase mothers' birth preparedness and complication readiness (38). Moreover, women who had antenatal care visits were more knowledgeable about maternal and neonatal complications (39). This increased knowledge could explain increased postnatal care checkups.

The study revealed that women who gave birth at healthcare institutions were 1.55 times more likely to have a PNC visit than women who gave birth at home. This is in line with other studies conducted in Ethiopia (19, 37, 40, 41), and Nepal (30). Giving birth in a health facility increases both women's awareness and knowledge of the benefits of neonatal checkups, provides better information on postpartum complications, increases access to healthcare services, and increases the mother's health-seeking behavior. Evidence suggests that education about postnatal care schedules leads to an increase in PNC visits (42).

Women who were aware of neonatal danger signs were 3.06 times more likely than women who were not aware of neonatal danger signs to have a PNC checkup for neonates. The findings are consistent with other studies conducted in various parts of the world (43, 44). This could be related to enhanced awareness of mothers on neonatal danger signs, which may increase those who seek healthcare (45). Understanding neonatal danger signs also assists women in identifying early warning signs of a neonatal problem, which increases neonatal care-seeking behaviors.

A strength of this study was the data taken from a large and representative sample size. A limitation of this study is that, because of its cross-sectional nature, it does not demonstrate a cause-and-effect relationship between the variables examined and the completion of neonatal checkups. Survey responses may also have been affected by social desirability bias.

CONCLUSION

In this study, the national PNC completion rate was very low at just 8.3%. PNC visit was associated with perceived distance from healthcare institutions, institutional delivery, having ANC visits, and being aware of neonatal danger signs. Our findings suggest that improving ANC visits, delivery in healthcare facilities, maternal awareness of neonatal danger signs, and access to health care, including through home visits, may improve rates of PNC in Ethiopia. Moreover, emphasis should be given to community-based newborn care packages, which have been implemented in Ethiopia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Permission was obtained to use the EDHS data from the measure DHS International Program, and approval data was also obtained. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was given.

AUTHOR CONTRIBUTIONS

BB, DB, DM, EC, and WA designed the study, interpreted the results, and prepared the manuscript. BB, DB, AE, DA, SD, GN, EA, SN, YT, and DJ analyzed, interpreted, and wrote the manuscript. TM reviewed and edited the manuscript. All authors were involved in design, data interpretation, and reviewed the manuscript.

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Maternal Undernutrition and Low Birth Weight in a Tertiary Hospital in Sudan: A Cross-Sectional Study

Jalal A. Bilal[1], *Duria A. Rayis*[2], *Ashwaq AlEed*[3,4], *Abdullah Al-Nafeesah*[3]* and *Ishag Adam*[5]

[1] *Department of Pediatrics, College of Medicine, Shaqra University, Shaqra, Saudi Arabia,* [2] *Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Khartoum, Sudan,* [3] *Department of Pediatrics, Unaizah College of Medicine and Medical Sciences, Qassim University, Unaizah, Saudi Arabia,* [4] *Department of Pediatrics, College of Medicine, Qassim University, Buraydah, Saudi Arabia,* [5] *Department of Obstetrics and Gynecology, Unaizah College of Medicine and Medical Sciences, Qassim University, Unaizah, Saudi Arabia*

Background: The World Health Organization set a Global Nutrition Target of a 30% reduction in LBW by 2025. Maternal malnutrition/undernutrition is among the most important modifiable risk factors for impaired fetal growth. This study investigates the effect of maternal undernutrition on LBW in Sudan.

Methods: A cross-sectional study was conducted at Saad Abuelela Hospital in Khartoum, Sudan, from May to October 2020. The sociodemographic and obstetric data of the women were gathered *via* questionnaire, and their mid-upper arm circumference (MUAC) was measured. Maternal undernutrition was defined as a MUAC of <23 cm.

Results: In total, 1,505 pairs of pregnant women and their newborns were enrolled in the study. The medians [interquartile (IQR)] of the age, parity, and gestational age were 27.0 (9.0) years, 1.0 (3.0), and 38.0 (2.0) weeks, respectively. The median (IQR) of the birth weight was 3,028.0 (690.0) g. Of the 1,505 participants, 182 (12.1%) delivered LBW infants. Multivariate logistic regression showed that MUAC [adjusted odds ratio (AOR) = 0.91, 95% confidence interval (CI) = 0.87–0.96] and gestational age (AOR = 0.79, 95% CI = 0.73–0.85) were negatively associated with LBW. The level of antenatal care <2 visits (AOR = 2.10, 95% CI = 1.30–3.57) was associated with LBW. Women with undernutrition were at a higher risk of delivering LBW infants (AOR = 1.66, 95% CI = 1.09–2.53).

Conclusion: LBW is a health problem in Sudan, and women with undernutrition were at a higher risk of delivering LBW infants.

Keywords: undernutrition, pregnant women, low birth weight, Sudan, cross sectional study

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***Correspondence:**
Abdullah Al-Nafeesah
a.alnafeesah@qu.edu.sa

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INTRODUCTION

It has been estimated that over 20 million deliveries have resulted in LBW infants (LBW; <2,500 g) annually; the vast majority of these LBW deliveries are in low- and middle-income countries (1). Several factors, such as infections, low education level, low income, and occupation, are associated with LBW (2–4). It has been found that about 3.6 million infants die (mainly in southern Asia and sub-Saharan Africa) during the neonatal period (1). The World Health Organization (WHO) set a Global Nutrition Target of a 30% reduction in LBW by 2025 (1). Maternal nutrition affects the growth of the fetus as well as birth and neonatal outcomes (5–8). Reports indicate that more than one-third of child deaths are caused by maternal and child undernutrition (9). Maternal malnutrition/undernutrition is among the most important modifiable risk factors for impaired fetal growth (9). Nutrition plays a fundamental role in health of pregnant women and the growth of fetuses. Poor maternal nutrition can lead to an increased risk of stillbirth, an increased risk of neonatal morbidity, death, and permanent deficits in growth and neurocognitive development (10).

Maternal undernutrition is a problem in developing countries (11). The prevalence of undernutrition among pregnant African women was 23.5% (12). It has been estimated that up to 20% of African women of reproductive age are undernourished (9, 13, 14).

Investigating the association between maternal undernutrition and LBW is vital for evidence-based interventions to reduce the burden of LBW. Several studies have assessed the association between birth weight/LBW and maternal undernutrition in African countries (15–19). LBW is a health problem in Sudan (20, 21). It has been reported that 12.5% of pregnant Sudanese women in Khartoum are undernourished (22). To the best of our knowledge, there are no evidence-based publications on the association between maternal undernutrition and LBW in Sudan. As such, this study was conducted to investigate the effect of maternal undernutrition on LBW in Sudanese women.

MATERIALS AND METHODS

This cross-sectional study was conducted at Saad Abuelela Hospital in Khartoum, Sudan, from May to October 2020.

Inclusion Criteria

Women with a single and alive newborn.

Exclusion Criteria

Women with multiple pregnancies, intra-uterine fetal death, delivering a baby with one or more congenital anomalies, and women with diseases known to influence the birth weight such as thyroid disease, diabetes mellitus, hypertension, antepartum hemorrhage, or any other chronic disease (**Figure 1**) were excluded.

After signing informed consent, data were collected by trained medical officers who graduated from medical schools. The socio-demographic and obstetric data were gathered and recorded face-to-face using a structured questionnaire about obstetric history (age, parity, gestational age, antenatal attendance, education level, miscarriage history, and employment). Gestational age was calculated using a combination of the dates of the last menstrual period and early pregnancy ultrasound.

Newborn weights were recorded within 1 h of delivery. The mother's mid-upper arm circumference (MUAC) was measured after delivery using a flexible non-stretchable standard tape measure. The circumference was measured at the mid-point between the tip of the acromion process of the scapula and the olecranon process of the ulna. Measurements were taken on the right arm to the nearest 0.1 cm (23). Maternal undernutrition was defined as a MUAC of <23 cm. Hemoglobin was measured (before delivery) using an automated hematology analyzer according to the manufacturer's instructions (Sysmex, KX-21, Japan). A Salter scale (which was checked for accuracy daily) was used to weigh the newborns immediately (by the staff) after birth to the nearest 10 g. The gender of each newborn was recorded.

Sample Size Determination

A sample size calculation for a cross-sectional study was applied and was estimated as 1,505 women using the recent prevalence (14.5%) of LBW in the study area (20). Thus, we assumed that the ratio of women with LBW to the women with no LBW was 1:6. Depending on our findings, we expect that 20.0% of the women who had LBW had undernutrition, and 12.5% of the women who had no LBW had undernutrition (22). This sample had a type I error of 5% and adequate power (80% power; $\beta = 0.2$).

Statistics

Data were entered into the Statistical Package for Social Sciences (SPSS) version 22 software (SPSS Inc.) for analysis. Continuous data (including MUAC) were checked for normality and were not normally disturbed. Therefore, the median [interquartile (IQR) range] was used to express their values. Categorized data were presented as frequencies and proportions. Multicollinearity (variance inflation factor, <4) was checked for but not detected. Univariate analyses were performed with LBW as the dependent variable and clinical obstetrics data [age, parity, employment, education level, antenatal care (ANC), MUAC, hemoglobin, gestational age, and newborn gender] as the independent variables. MUAC and undernutrition were entered one by one in each model. Variables with a $p < 0.20$ univariate analysis were entered to build the multivariable logistic regression models, and backward-stepwise regression was used for adjustment. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Basic Characteristics of the Participants

A total of 1,505 pairs of pregnant women and their newborns were enrolled in the study. The median (IQR) of the age, parity, and gestational age was 27.0 (9.0) years, 1.0 (3.0), and 38.0 (2.0) weeks, respectively. Half of these women were primipara (170, 50.1%). The vast majority of these women were housewives (1,331, 88.8%), and over half (836, 55.5%) had an education level ≥ secondary school. In total, 106 (7.0%) attended ≥ three antenatal visits, and 328 (21.8%) of the studied women had a history of miscarriage. Three hundred and twelve (20.7%) women had a cesarean delivery.

The median (IQR) of the birth weight was 3,028.0 (690.0) g. Of 1,505 participants, 182 (12.1%) delivered LBW infants.

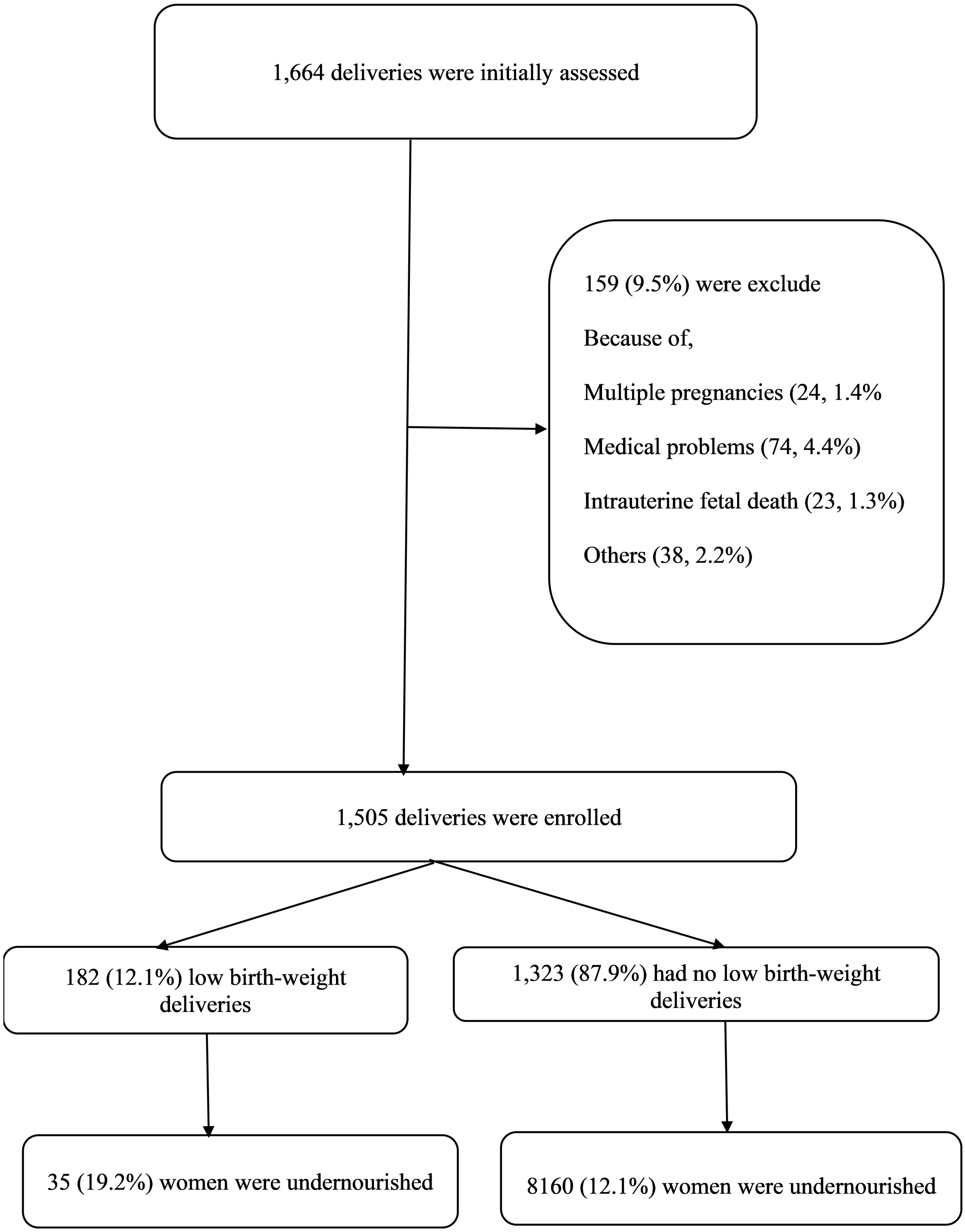

FIGURE 1 | The flow chart for the study.

The MUAC, gestational age, ANC, and education levels were significantly lower in women who delivered LBW infants. No significant difference was found in age, parity, hemoglobin levels, residence, employment, miscarriage history, and newborn gender between the two groups (**Table 1**).

The median (IQR) of MUAC was significantly lower in women who gave birth to LBW infants [10.0 (6.5) ng/mL vs. 18.3 (22.1) ng/mL]. In total, 35/182 (19.2%) women with LBW infant and 160/1,323 (12.1%, $p = 0.010$) women who did not deliver a LBW infant had undernutrition.

Multivariate logistic regression showed that MUAC [adjusted odds ratio (AOR) = 0.91, 95% CI = 0.87–0.96] and gestational age (AOR = 0.79, 95% CI = 0.73–0.85) were negatively associated with LBW. A level of antenatal care <2 visits (AOR = 2.10,

TABLE 1 | Univariate analysis of the factors associated with low birth weight in Khartoum, Sudan, 2020.

Variables	Low birth weight (182)	No low birth weight (1,323)			
	Median (interquartile range)		OR	95% CI	*p*-value
Age (years)	26.5 (11.0)	27.0 (9.0)	0.98	0.95–1.01	0.197
Parity	1 (3.0)	1 (3.0)	0.99	091–1.05	0.987
Mid-upper arm circumference, cm*	25.2 (5.0)	26.0 (5.0)	0.91	0.88–0.96	<0.001
Hemoglobin level (g/dl)	10.7 (1.9)	10.5 (1.6)	1.02	0.91–1.56	0.637
Gestational age, weeks	38.3 (3.0)	38.3 (3.0)	0.79	0.73–0.85	<0.001
	Number (percentage)				
Education level					
Secondary or higher	85 (46.7)	751 (65.8)	Reference		
Primary or lower	97 (53.3)	572 (43.2)	1.49	1.09–2.04	0.001
Residence					
Urban	93 (51.1)	722 (56.6)	Reference		
Rural	89 (48.9)	601 (45.4)	1.15	0.84–1.56	0.378
Employment					
Housewives	163 (89.6)	1,168 (88.3)	Reference		
Non-housewives	19 (10.4)	155 (11.7)	0.87	0.53–1.45	0.614
Antenatal care			1.16	0.68–1.88	0.614
≥2 visits	154 (84.6)	1,245 (91.4)	Reference		
<2 visits	28 (15.4)	78 (5.9)	2.90	1.82–4.61	<0.001
History of miscarriage					
No	141 (77.5)	1,036 (78.3%)	Reference		
Yes	41 (22.5%)	287 (21.7%)	1.05	0.72–1.52	0.789
Undernutrition*					
No	147 (80.8)	1,163 (87.9)	Reference		
Yes	35 (19.2)	160 (12.1)	1.73	1.51–2.59	0.008
Gender					
Female	101 (55.5)	660 (49.9)	Reference		
Male	81 (44.5)	663 (50.1)	0.80	0.58–1.09	0.163

*CI, confidence interval; OR, odds ratio. *stand for median.*

TABLE 2 | Logistic regression analysis of the factors associated with low birth weight in Khartoum, Sudan, 2020.

Variables	Adjusted values		
	OR	95% CI	*p*-value
Age, years	1.01	0.97–1.04	0.536
Mid-upper arm circumference, cm**	0.91	0.87–0.96	<0.001
Gestational age, weeks	0.79	0.73–0.85	<0.001
Education level			
Secondary or higher	Reference		
Primary or lower	1.40	0.97–2.02	0.067
Antenatal care			
≥2 visits	Reference		
<2 visits	2.10	1.30–3.57	0.003
Undernutrition*			
No	Reference		
Yes	1.66	1.09–2.53	0.018
Gender			
Female	Reference		
Male	1.37	0.98–1.90	0.059

CI, confidence interval; OR, odds ratio.
**These were entered one by one (one per model).*
***Adjusted for age and education.*

95% CI = 1.30–3.57) was associated with LBW. Women with undernutrition were at a higher risk of delivering LBW infants (AOR = 1.66, 95% CI = 1.09–2.53), **Table 2**.

DISCUSSION

In this study, 12% of deliveries resulted in a LBW infant. The prevalence of LBW in our study is comparable with the LBW prevalence (14.3%) which was previously reported in the same hospital (20) and in different hospitals in neighboring Ethiopia (24–26). The prevalence of LBW in our study is lower than the LBW prevalence (21.6%) reported at the Debre Markos Hospital (Ethiopia) (27). However, the prevalence of LBW in the current study is much higher than the LBW prevalence in Ghana (9.7%) (28) and in Nigeria (7.3%) (29). Notably, the prevalence of LBW in our study is lower than the pooled LBW prevalence in Sub-Saharan Africa (9.76%) recently reported in a meta-analysis (30). The LBW prevalence difference between the current study and a later one can be explained by the difference in study design and the sociodemographic characteristics of different settings. It is worth mentioning that a high LBW prevalence indicates a difficulty in achieving the World Health Assembly's (WHA's) target of reducing the LBW prevalence to ≤10.5% by 2025 (31).

In the current study, pregnant women who had attended less than two ANC visits were at a 2.10 higher risk of delivering an LBW newborn. This is consistent with the previous studies conducted in Sudan (32), Ethiopia (33), Kenya, Zimbabwe (34), and Tanzania (35). Moreover, in their meta-analysis, Tessema et al. reported that ANC visits were associated with reduced LBW occurrence (30). This can be explained by the opportunity for ANC to access various preventive measures (nutritional counseling and health provisions, such as iron supplements) and screen for any possible problems that might lead to LBW.

In the current study, MUAC (AOR = 0.91) was negatively associated with LBW. Women with undernutrition were at a higher risk of delivering LBW (AOR = 1.66) newborns. Several previous studies have shown that maternal undernutrition is associated with LBW (15–17). In their 2017 meta-analysis of 4,633 participants from 13 studies, Cates et al. reported that the risk of delivering a baby with LBW was associated with low MUAC (relative risk = 1.60) (18). In 2011, a meta-analysis by Han et al. of 78 studies involving 1,025,794 women found that underweight women were at an increased risk of having LBW infants (19).

Our finding of an association between gestational age and LBW is in agreement with the results from neighboring Ethiopia (15).

We reported no association between maternal age, residence, newborn gender, maternal Hb and delivering LBW infants. Previous studies have shown that maternal Hb (17), maternal age, rural residence, and female gender were significantly associated with LBW (15, 33).

The other assessment tools for the micronutrient deficiencies during pregnancy are costly and technically difficult. Anthropometrics measurements, such as MUAC, are useful in assessing the malnutrition state. Unlike body-mass index, MUAC does not change during pregnancy; therefore, it seems to be the best tool for assessing the nutritional status during pregnancy (36, 37).

Strength and Limitations of the Study

The present study has some strengths including its large sample and taking newborn weight within 1 h of delivery. However, our study has limitations such as it was a hospital-based study, which might not reflect what was going on in the community. The study was conducted at a single hospital, the finding might not be generalizable to the entire birth cohort in the area. The cross-sectional nature of the study makes it difficult to draw inferences about the cause–effect relations among study variables. The number of ANC visits was taken from verbal response of respondents. There might be recall bias as respondents had to remember their ANC visits. In addition, important variables like physical activity and dietary diversity were not assessed.

CONCLUSION

LBW is a health problem in Sudan. Women with undernutrition are at a higher risk of delivering LBW infants.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research and Ethical Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Khartoum, Sudan (# 2020, 04). Informed consent was given by the participants. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JB designed the research, analyzed the data, and interpreted the results. AA-N and AA designed the research and wrote the manuscript. DR conducted the research, analyzed the data, and wrote the manuscript. IA designed the research, conducted the research, and analyzed the data. All authors read and approved the final manuscript.

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Improving Post-discharge Practice of Kangaroo Mother Care: Perspectives From Communities in East-Central Uganda

Doris Kwesiga[1,2,3]*, Phillip Wanduru[1,3,4], Eric Ssegujja[1], Justine Inhensiko[3], Peter Waiswa[1,3,4] and Linda Franck[5]

[1] Department of Health Policy, Planning and Management, School of Public Health, Makerere University, Kampala, Uganda, [2] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden, [3] Centre of Excellence for Maternal Newborn and Child Health Research, Department of Health Policy, Planning and Management, School of Public Health, Makerere University, Kampala, Uganda, [4] Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden, [5] Department of Family Health Care Nursing, University of California, San Francisco, San Francisco, CA, United States

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Edited by:
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***Correspondence:**
Doris Kwesiga
dknnkwesiga@gmail.com

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Introduction: Kangaroo mother care (KMC) is among the most cost-effective and easily accessible solutions for improving the survival and wellbeing of small newborns. In this study, we examined the barriers and facilitators to continuity of KMC at home following hospital discharge in rural Uganda.

Methods: We conducted this study in five districts in east-central Uganda, within six hospitals and at the community level. We used a qualitative approach, with two phases of data collection. Phase 1 comprised in-depth interviews with mothers who practiced KMC with their babies and caretakers who supported them and key informant interviews with health workers, district health office staff, community health workers, and traditional birth attendants. We then conducted group discussions with mothers of small newborns and their caretakers. We held 65 interviews and five group discussions with 133 respondents in total and used a thematic approach to data analysis.

Results: In hospital, mothers were sensitized and taught KMC. They were expected to continue practicing it at home with regular returns to the hospital post-discharge. However, mothers practiced KMC for a shorter time at home than in the hospital. Reasons included being overburdened with competing domestic chores that did not allow time for KMC and a lack of community follow-up support by health workers. There were increased psycho-social challenges for mothers, alongside some dangerous practices like placing plastic cans of hot water near the baby to provide warmth. Respondents suggested various ways to improve the KMC experience at home, including the development of a peer-to-peer intervention led by mothers who had successfully done KMC and community follow-up of mothers by qualified health workers and community health workers.

Conclusion: Despite wide acceptance of KMC by health workers, challenges to effective implementation persist. Amid the global and national push to scale up KMC, potential difficulties to its adherence post-discharge in a rural, resource-limited setting remain. This study provides insights on KMC implementation and sustainability from the perspectives of key stakeholders, highlighting the need for a holistic approach to KMC that incorporates its adaptability to community settings and contexts.

Keywords: kangaroo mother care (KMC), pre-terms, Neonatology, low and middle-income countries (LMIC), Uganda (Sub-Saharan Africa)

INTRODUCTION

The World Health Organization (WHO) recommends kangaroo mother care (KMC) as a high-impact but a low-cost intervention that improves the survival and development of small babies in resource-limited settings (1, 2). The components of KMC include early, continuous, and prolonged skin-to-skin contact between the mother or a caregiver and a baby; exclusive breastfeeding; early discharge; and continued follow-up of the baby at home (3). Recent systematic reviews have demonstrated that KMC, when implemented consistently, results in a significantly lower risk of death for small babies (4, 5). Other notable benefits of KMC included reduced risk of infections, reduced risk of re-admission, and improved weight gain (4, 5). For mothers and their families, there were benefits like positive emotions, less pain, increased breastmilk production, increased esteem and sense of control of their situation, and parental role identity. The safety and affordability of KMC have also been proven (6).

Despite the benefits of KMC in improving survival among small newborns, its uptake remains low (7). A survey conducted in Uganda in 2014 among 17 health facilities across the country indicated that only one facility had integrated KMC into its routine care (8). Another study at one of the biggest referral hospitals in Uganda found that continuous skin-to-skin contact in the first week of birth was 3 hours, which is below the recommended 20 hours [9].

Reasons for the low uptake of KMC are fairly well-documented. A systematic review on barriers and enablers of KMC found that in low- and middle-income countries, the biggest challenges mothers faced included lack of help with implementing KMC, perceptions of negative health worker attitudes, and lack of awareness of KMC (10). Physical discomfort was another problem noted, especially pain and fatigue. Mothers complained about backache from sleeping upright and having to do it for up to 24 hours at a time (6, 10). An observational study conducted in Uganda highlighted challenges of practicing KMC within health facilities, and these included a lack of space to implement KMC because of overcrowding, a lack of privacy, and a lack of infrastructure like seats for KMC; thus, some women had to sit on the floor (9). Another systematic review found that facilities had no designated KMC space, inadequate beds and seats for KMC, and other supplies like baby wraps (11).

Although there has been advancement in the understanding of barriers and enablers of KMC within facilities, there is limited research on the continuity of KMC post-discharge in resource-limited settings like Uganda. Early discharge is a pertinent component of KMC, but this is most useful if there is continuity of KMC at home. Therefore, in this study, we aimed to examine the barriers and facilitators to continuity of KMC at home following hospital discharge in rural Uganda.

MATERIALS AND METHODS

Study Design

This was a multi-method qualitative study with a phenomenological approach. We conducted in-depth interviews (IDIs), key informant interviews (KIs), and group discussions. The study had both facility and community-based components. It took place over 1 year, with data collection done in phases: phase 1 included IDIs and KIs conducted in December 2016 and January 2017 and phase 2 focused on group discussions from May to July 2017.

In the group discussions, we used the principles of participatory learning and action (PLA) (12), where the study team engaged mothers and their support persons in a deductive process of identifying solutions to the problem of sub-optimal implementation of KMC at home. As described in **Table 1**, we used various problem-solving techniques including a "problem tree," a "spider diagram," and a "net to keep me safe."

Study Setting

The study was carried out in Busoga region, a predominantly rural area situated in east-central Uganda. It has a population of about three million or 10% of Uganda's population residing in an area of ∼7,100 square miles. The Busoga region has 10 administrative districts: Iganga, Mayuge, Bugiri, Kamuli, Kaliro, Namutumba, Namayingo, Luuka, Buyende, and Jinja.

The facility-based component was conducted in six hospitals in eastern Uganda, which are a mix of four government- and two missionary-founded hospitals. These hospitals are spread out across five districts. Together, they had ∼21,000 deliveries per year between 2016 and 2019. They all provide maternal and newborn services, including delivery and resuscitation of babies (**Figure 1**).

Participant Selection

All participants, including mothers, support persons, community leaders, village health team (VHT) members, traditional birth attendants, district health officers (DHOs) in-charge of maternal and child health, and health workers were purposively selected.

TABLE 1 | Group discussion approaches.

Problem tree	Spider diagram	A net to keep me safe
The "Why" question is asked until the root cause of the problem is identified. *Example*: Mothers complain about difficulties while practicing KMC. Why? *Steps* 1. Draw a trunk representing the core issue and the roots and rootlets representing direct and indirect causes, and branches representing direct and indirect effects 2. Identify the causes at one or several levels and leave out the effects 3. Restrict the analysis to major causes and effects only 4. Don't consider causes and effects that strengthen each other through direct or indirect connections 5. Ask why between four and five times to understand the immediate or underlying causes of the problem 6. Identify the effect of the identified problem and include them as tree branches and leaves. Probe particularly for failure in uptake and adherence/consistent practice of KMC	The spider diagram was used to provide a non-stigmatizing way of identifying key problems that mothers experience during the practice of KMC. In the process, it will assess which of these problems is greater, why, and what opportunities exist for KMC practice (facilitators). Step 1: Draw the shape of a spider. In the middle of the spider's body is where the topic, i.e., problems and opportunities for practicing KMC will be written. Discuss these Step 2: After the mothers are done with the drawing, a discussion about the drawing will follow, for example asking the mothers: • Which of the problems are easier or harder to address? • What type of action could be taken to address the problem? • Who should take the action?	The objective of this tool was to help the mothers identify and understand the networks and stakeholders that can be relied on for support during the practice of Kangaroo Mother Care (KMC). They also reflected on how to improve KMC practice. Introduction: When we are faced with the challenges of having to practice KMC as mothers, there are some people, groups, or organizations that we will always run to for help who will listen to us or give us support. These are like nets that will catch us when we fall. In this exercise, you will show us who these people are in your family, in your community, and in the health facility. The mothers should also suggest ways in which the KMC experience can be made better, within hospitals and at the community level, and who should be involved in these processes. Help them devise strategies on how to approach people on the net. *We did not do this exercise using an actual net on the ground as planned, but rather used discussions only

Mothers of pre-term or low-birth weight (LBW) babies were eligible to participate. Pre-term babies were defined as babies born before 37 completed weeks of gestation (13). Low-birth weight was defined as weight at birth less than 2,500 g (14). Mothers were selected from a pool of those who were practicing KMC in the hospitals at the time of the study and those who had practiced KMC in the past year in the hospitals (whether they completed it or not). Some were recruited in hospitals, where research assistants with the help of health workers recruited those who were practicing KMC at the time of the study from the wards. Others were identified when they came to the hospital for follow-up care for their babies. The last group of mothers who were at home were identified through the hospital record books and contacted using the telephone numbers they had registered.

Support persons were those who helped the mothers perform KMC after birth. These were family members, including siblings, husbands, and grandmothers. They were approached by the research assistants in person (those who were in the hospital with mothers at the time of the study) or by telephone, through the number given by the mothers. In some cases, mothers, often those who had twins or triplets, came for the group discussions with the support persons. Health workers were nurses in the six hospitals, specifically those in-charge of the maternity or newborn care unit (NCU) section in each hospital. Traditional birth attendants are those who offer informal "midwife" services in the communities, typically in their own homes. The research team was informed about these by different sources who knew about them—mothers who used them and VHTs. The VHT members are voluntary community health workers (CHWs) chosen by communities and trained by the government to offer support to health services in communities by providing certain basic healthcare, for instance, malaria treatment. The ones we interviewed were attached to the hospitals of study and were recommended by the health workers we interacted with. The DHOs supervise program implementation in the district, and we selected the assistant DHO in each district because they oversee maternal and child health.

Doctors were not among the study respondents. This is because, at the time of the study, none of them were involved in initiating, implementing, and/or supervising the implementation of KMC. Furthermore, it was difficult to get doctors to participate in interviews because none of them were assigned exclusively to the NCU; they only came in for brief periods of time to conduct clinical rounds before moving on to other parts of the hospital.

Data Collection

In the communities, IDIs were conducted in the homes of the respondents. Some IDIs were held at the hospitals, with admitted mothers and those who came for follow-up care. The group discussions with mothers and support persons were held at or near the health facilities. The KIs with health workers were conducted at the health facilities. The VHTs were found at the health facilities, traditional birth attendants in their homes, and district health office staff in their places of work.

A group of seven research assistants, familiar with qualitative methodologies and with prior experience in maternal and child health research, conducted the IDIs and KIs. The group discussions were facilitated by three researchers also experienced in qualitative research methods, familiar with the study area, and with prior working knowledge of maternal and child health

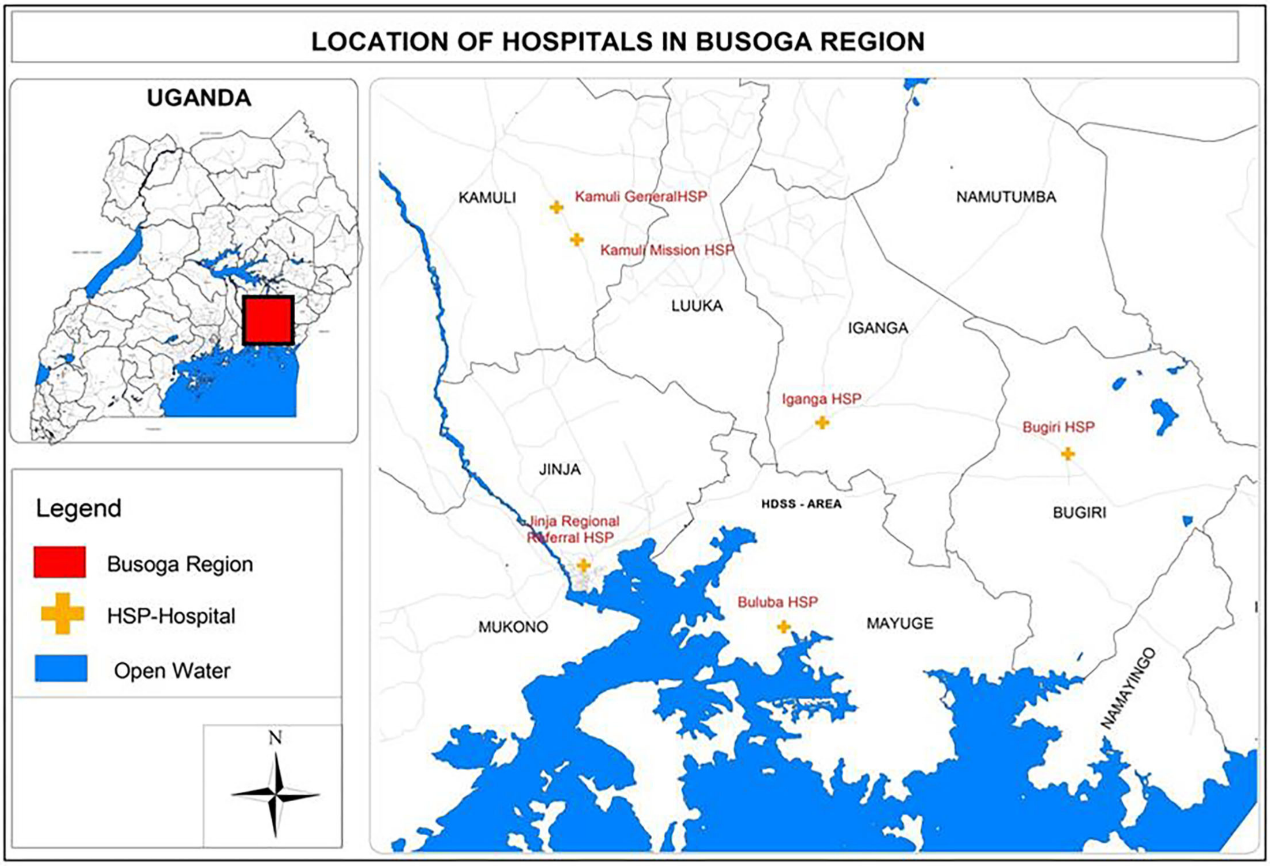

FIGURE 1 | Hospitals and communities where study was conducted.

research and programming. The research assistants were trained on the study protocol before study commencement, and tools were discussed in both English and *Lusoga*, the most commonly spoken language in the study area. Interview guides informed by the literature and the study team's experience of the topic were developed by DK and reviewed by LF, PW, and ES for each of the different stakeholder groups. These were pre-tested, and minor revisions were made. Guides included questions on knowledge of care for pre-term/LBW babies; knowledge of KMC; the practice of KMC and the barriers and enablers therein; acceptability of KMC; and recommendations.

After the IDIs and KIs were completed, an initial analysis of the data collected was conducted to inform the group discussions. This resulted in slight modifications to the group discussion phase, followed by one group discussion in each district. The activities used to engage participants in group discussions (12) are elaborated in **Table 1**. All the interviews and group discussions were audio recorded, with field notes taken during the process after obtaining the consent of the participants. The interviews ranged from 40 min to 1 hour and 10 min in duration, while the group discussions lasted 2 hours. Upon completion of the interview, the audios were transcribed and translated into English, where this was not the study language. Finally, direct observations of KMC in the different settings (hospital and home) were conducted and documented in field notes by the researchers, with particular attention to the institutional, practical, and social support available to and used by mothers. Saturation was determined by the study team after having reached a point where no new insights were emerging and similar meanings were seen across the different data collection methods.

Data Analysis

An interpretative paradigm was used in this study as well as thematic analysis (15). Inductive and deductive coding approaches were both used through an iterative process. Analysis of the IDIs and KIs was done by three people. While each coder worked independently, the team regularly held a series of meetings to discuss the codes and together agree on emerging themes; two of the coders used Atlas QI, a qualitative data management software to code the transcripts, while one conducted data analysis manually. For the group discussions, the first level of analysis was done during the discussion sessions with participants, followed by further analysis by the principal investigator (DK). Field and observation notes supplemented and integrated the analysis and the discussion section of this study.

TABLE 2 | Number of interviews and respondents.

Category (A)	Number interviewed
Mothers	14
Support persons/caregivers	10
Traditional birth attendants	6
Health workers	13
Assistant district health officers in charge of maternal and child health	5
Community leaders	7
Village health team members	10
Total	65
District (B)	**Number present in group discussion**
Jinja	8
Iganga	20
Kamuli	18
Mayuge	12
Bugiri	10
Total	68

All analyses aimed to discover commonly recurring themes and outliers. Triangulation was enhanced through the comparison of results between individual respondents, as well as between the different stakeholder groups and data collection methods, for areas of agreement and disagreement. Emerging themes were discussed among the study team members to identify underlying meanings. During the study team discussions, we analyzed topics for areas with greater consensus.

Ethical Approval

This study received ethical approval from the Higher Degrees, Research and Ethics Committee at Makerere University, School of Public Health as well as Uganda National Council for Science and Technology. The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before participation in the study. Efforts to protect the privacy and confidentiality of participants' identities and information were undertaken.

RESULTS

The results presented are from 65 respondents and five group discussions, whose details are shown in **Table 2**.

Knowledge About Kangaroo Mother Care Practice

Overall, the mothers understood KMC practice, reflected in their knowledge of its implementation. They reported that KMC refers to the wrapping of the baby skin-to-skin on the chest of the mother or any other caretaker in a way that positions the head to ensure breathing. The other critical aspects mentioned were monitoring the baby's temperature, breastfeeding or cup feeding when the baby cannot suckle, maintaining good hygiene, and returning to the health facility for follow-up appointments or when they noticed adverse signs. However, there were some gaps in knowledge among the mothers, for instance, in the number of hours KMC should be done, when exactly it should be terminated, and some of the other practicalities of KMC.

Three major themes that emerged as common and cutting across all stakeholder groups are presented below, with sub-themes discussed under each. These are (1) implementation of kangaroo mother care in health facilities—this is happening, but more support is needed; (2) continuity of kangaroo mother care at home post-discharge—this is predominantly difficult; and (3) recommendations to improve kangaroo mother care.

Although our study focuses on post-discharge, that part of KMC is a continuation of what occurs within the health facility. Therefore, we included a theme on the implementation of KMC in health facilities to present the basis of our study and explain the context, particularly for the reader who may not know what occurs in the Ugandan health facility context. We thus started with brief highlights of KMC in the health facilities and then focused on the community and the suggestions from participants.

Theme 1: Implementation of Kangaroo Mother Care in Health Facilities

Our study indicates how KMC is initiated, the aspects of its implementation, and barriers to implementation in facilities. We found that KMC was always initiated by the health worker, after ascertaining the stability and health of the baby. The health worker then taught the mother about it and supported her to position the baby correctly on her chest. In all six hospitals, mothers and health workers revealed that KMC was done intermittently. Mothers revealed that they would do KMC for between 30 min and 2 hours continuously and then stop for a few hours before resuming. Most KMC was practiced in a special KMC room, although in one hospital, we observed mothers performing KMC in the special care unit (SCU). While mothers were predominantly the ones doing KMC, in the minority of cases, the sister to the mother of the pre-term helped her do KMC in the hospital, which was more common among those who had multiple births. Healthcare workers reported that occasionally, fathers would also actively get involved and perform KMC. One mother described her daily KMC routine:

> *Yes, and I would do KMC and breast feed. For KMC, they would say 30 minutes and you give us our things. They would wrap the baby here [respondent demonstrates using her baby facing her how she used to do KMC] and they would tell me to go lie with it on the bed like this [demonstrates lying on her back] and it is here [in the chest]. From here [KMC], it would be taken back to their machine. (Mother, Iganga district)*

To support the implementation of KMC during admission, there was voluntary, informal peer-to-peer support, where mothers who had successfully started KMC supported and guided those who were new to it. This approach was encouraged by health workers as well.

There is one instance a mother delivered a baby weighing 1.5 kg from a clinic and she brought it here because it wasn't feeding so I gave her an example from another mother, and they talked, and she liked the idea (Health worker, Mayuge district)

Health workers in special care units (SCUs) thought positively about KMC as they had seen it produce favorable results. They therefore actively encouraged mothers to do it for small babies.

Barriers to Implementation of KMC in Health Facilities

Barriers to KMC implementation in the six healthcare facilities were classified into three main categories: human resource challenges, infrastructural inadequacies, and lack of support for mothers. The first two were mentioned by health workers, mothers, and support persons, while the third was mentioned by mothers and health workers.

Human resource challenges included understaffing, especially of NBUs and high staff turnover. Therefore, NBU staff could only dedicate a limited amount of time to teaching and monitoring the implementation of KMC for each mother and/or support person. This resulted in gaps in knowledge and practice of KMC in the NBU. In addition, hospitals have a policy of yearly rotations of nurses to other units. The incoming nurses were often not competent in KMC, and thus, there was a reduction in capacity to implement KMC after rotations. Most health workers reported that they had not been taught about KMC while still at school and therefore relied on externally organized refresher courses that targeted NBU staff.

We had a workshop on care of preterm/LBW babies; this workshop took place I think around 2013 organized by Makerere MANeSCALE group and it was participatory, whereby we could use models then at the same time we came to the wards to practice it on these mothers because we had some mothers with preterm babies already in the ward. (Health worker, Kamuli district)

Infrastructural inadequacies: Multiple challenges included small and crowded KMC rooms, few adjustable beds, and no special KMC chairs, which affected the comfort and the ability to do KMC for long hours. Mothers reported immense fatigue and pain from KMC as a result. Health workers explained that sometimes mothers had to be in the general maternity ward if the KMC room was full, and this was also observed in one hospital by the research team. Health workers explained that this was a potential source of infection for the babies. Poor hygiene and sanitation facilities also reduced the safety and effectiveness of KMC, and mothers protested about this.

Lack of support for mothers: Most mothers complained about the hospitals not providing food to patients, and this was corroborated by some health workers. They therefore had to look for their own food, and this was worse for mothers who were alone in the hospital because, as both mothers and health workers explained, they would have to stop KMC for a few hours to get food to eat, which affected their KMC.

Theme 2: Continuity of Kangaroo Mother Care at Home Post-discharge

Discharge, according to some health workers, was on average done when the baby was stable and progressing and when they were confident that the mother had learned how to do KMC, usually two or more weeks after birth. However, in a few cases, mothers reportedly asked to be discharged early due to various challenges like not having a caretaker for their other children at home as well as the accumulating hospital bills. Prior to discharge, health workers explained that they encouraged mothers to continue KMC at home.

Implementing KMC at Home

Discussions with mothers revealed that on arrival at home, most of the women tried to practice KMC as advised. However, they reported that they were often unable to do it as much as they had done in the hospital. Mothers revealed that at home, KMC was done for fewer hours, although it was still skin to skin as taught. More so, they explained that they did KMC more consistently at night than during the daytime. Mothers also reported observing the required practices for hygiene maintenance and control of infections, including washing the baby's clothes frequently and limiting the number of people visiting. Predominantly, it was still done by the mother herself, except in one case where the father of the baby was helping his wife to do it at home. However, we also identified two mothers who said that they stopped practicing KMC as soon as they left the hospital.

Specific challenges to the continuity of KMC at home were clearly identified in the data. These are presented under three broad areas: lack of community follow-up after discharge, home/family-level challenges, and inadequate knowledge about KMC.

Lack of Community Follow-Up After Discharge

We learned that after discharge, there was no functional community-based follow-up system by health workers. According to the model of care offered when the study was done, health workers explained that mothers doing KMC were expected to return to the hospital to bring their babies for follow-ups, information confirmed by the mothers. Mothers and their babies were not followed up at home by health workers after discharge, predominantly due to a lack of resources to do so, as explained by health workers in the various districts. Additionally, health workers emphasized being overwhelmed with responsibilities in the hospital and not having time to do individual follow-ups. Mothers also reported that CHWs did not follow them up in the community either. Indeed, the CHWs we spoke to did not know much about KMC practice and did not highlight helping mothers at home with KMC as one of their roles.

Unfortunately, some babies got sick at home, before the date given for their return to the hospital, as mothers said, and as the research team observed in the field. More so, some mothers could not afford transport to return for care often, especially if they lived far from the hospital. This was mentioned by both the health workers and mothers. Indeed, health workers said that it sometimes led to the mother–baby pair dropping out of follow-up care at the health facility or coming less regularly. One health worker explained that by 6 months, very few mothers were bringing back babies for the scheduled checks, especially when the baby appeared to be doing well. Health workers explained that previously under some projects, the mothers were followed up in the community but once these projects ended, the process was unsustainable.

> *....when I was discharged, I was given appointment dates for going back in hospital to examine the baby, but they did not make follow-up at home to check on me.... (Mother, Kamuli district)*

Home/Family-Level Challenges

There were four main barriers to KMC practice at home. The first was the continuation of dangerous practices used to care for pre-term babies at home, despite KMC. Mothers and support persons revealed that they sometimes resorted to other interventions at home, beyond KMC. For instance, both in group discussions and IDIs with mothers and support persons, they explained that occasionally charcoal stoves were lit in the room in which the baby was, in order to provide warmth. Another common practice was putting hot water in plastic cans and placing these around the baby for warmth. Additionally, one mother reported giving herbs to her pre-term baby once she was home and abandoning KMC altogether. In a few instances, mothers and caretakers revealed that health workers had warned them against the use of charcoal stoves to produce warmth.

> *...so, when I was discharged from hospital, I stopped doing it [KMC] and I even didn't go for follow-ups though I was given appointment dates. According to me the baby was okay, so there was no need of going to hospital and struggling with that method of kangaroo mother care, I just used our local herbs, and my baby is healthy (Mother, Kamuli district)*
>
> *You get water in a small jerrican, you put water here, there, and there [demonstrates on the ground how the water is put on all sides of the baby] and there is water on all the sides, and you put a charcoal stove nearby to make the baby warm with moderate fire (Mother, Iganga district)*

Gender roles and societal expectations toward mothers were other hindrances. Most women we interviewed in this study reported that they were expected to continue with their usual domestic chores once back at home, regardless of the fact that they had a pre-term baby to look after and needed to continue KMC. The majority of mothers described having to cook, clean, wash clothes, and look after animals and other children, as well as their husband/partner. Health workers corroborated the information about the heavy duties that the mothers had at home. Mothers sometimes asked to be discharged earlier, although they were still learning KMC because they had left their other children at home, and they needed to return to care for them. There was often only limited support for mothers doing KMC at home. Amid the many chores, most mothers explained that they did not have any social or in-kind support with this workload and health workers reiterated this. Being a predominantly rural setting, most mothers could not afford to hire somebody to help them at home with their chores. Those who had been supported by family members in the hospital often saw them depart on discharge, back to their own homes.

> *There are some activities that out compete the skin-to-skin practice and the treatment that you could give to the baby. For example, taking goats to the field, washing clothes, cooking, fetching water, collecting firewood, maybe you have a business, and you want to work (Mother, Iganga district group discussion)*

Financial challenges were another key issue, which was particularly the case for mothers previously engaged in income-generating activities. Most mothers emphasized that KMC resulted in a loss of productivity and income on the part of the mother, who was often unable to engage in whichever economic activity she may have previously been doing. This was because KMC and care for a pre-term baby generally required a lot of time and commitment, and so the mother could hardly do anything else. There were a few outliers among participants, where men were actively involved in KMC and in supporting their wives/partners at home. While supportive of the mother's health and sustainment of KMC, this reduced the men's ability to work as regularly as they previously did, resulting in reduced income.

Mothers revealed challenges with the physical performance of KMC. The majority explained that it was painful to implement and was cumbersome for mothers who had undergone a cesarean section. It caused backache and chest pain and was tiresome. They explained that sitting upright or lying flat on the bed to do KMC increased pain and fatigue. These physical challenges led to mothers performing KMC for a shorter time, especially when there was inadequate support for KMC.

> *Yes, there is real pain, too much backache, and you even feel it hard. The back really pains like a boil and even the chest pains and by time the baby is removed from the chest you are almost crying. (Iganga district group discussion).*

As a result of the multiple difficulties mentioned, the mothers reported psychosocial challenges, including stress, depression, and discouragement. Health workers confirmed this as a major problem. The mother barely had time for her self-care, was often isolated with the baby, and barely socialized with other people.

Inadequate Knowledge About KMC

We found a gap in knowledge about KMC among the mothers, support persons, and community members. For example, some mothers and support persons were uncertain about the recommended number of hours KMC should be done, when it should be terminated, and how it should be done. In some cases, the mothers themselves also acknowledged their own inadequate KMC knowledge. Almost all mothers mentioned that their first interaction and exposure to KMC practice were at the health facility by the health workers after the birth of their index pre-term baby. Only two mothers indicated having heard about it before delivery of the index pre-term baby. One among these had a sister who previously gave birth to a pre-term baby, and the other was taught about KMC by a relative. Similarly, support persons had minimal information on KMC. Community members who were playing a role in maternal and newborn health, for instance, the traditional birth attendants and VHTs, were equally lacking in information about KMC.

Theme 3: Recommendations to Improve Kangaroo Mother Care

As part of our participatory research approach to this study, we purposively explored the recommendations and preferences of community members for making KMC easier to implement and to ensure an increased uptake. Under this theme, we present three of the prominent improvements to address the uptake and sustainability of KMC as recommended by the participants.

Community Follow-Up

The follow-up of mothers in the community was noted as an enabler to better KMC uptake and acceptability by participants, including health workers, mothers, support persons, and VHTs. Among the suggestions on how the community follow-up could be done was the use of VHTs, including facilitating them with transport to do this job. As a health worker from Mayuge pointed out, the VHTs could conduct health education, while others agreed that they could check the progress of the pre-term baby. A VHT from Kamuli also agreed with VHTs following up the progress of mothers at home. The need for the VHTs to be trained on KMC so they can teach mothers within the community to do it as well as monitor their adherence was emphasized. However, the health workers supported VHT involvement only as part of the post-discharge care after the mother had learned about KMC in the hospital. They were not supportive of the idea of VHTs initiating KMC for babies born within the community, due to other intricate care needed for pre-term babies, especially within the first days of life.

Another suggestion for the follow-up from a caretaker was the option of health workers making phone calls to the mothers. The health workers were also supportive of the idea of health workers at lower level health facilities being involved in community follow-ups, provided that they received adequate training.

> *Health workers should help and make home follow ups or making a call to check on the baby so that the person meant to practice it [KMC] must do it so when these babies keep on surviving then people will be motivated to practice the method (Caregiver, Kamuli district)*

Development of a Peer-to-Peer Intervention

Some of the mothers who had successfully done KMC and seen its positive effects on their babies eagerly recommended that they could assist and teach mothers who were new at KMC what to do. They volunteered and expressed their willingness to do so, including the provision of knowledge and practical demonstrations. Some health workers also felt that success stories of mothers who had successfully done KMC could be used as positive motivation and demonstration to others. One health worker envisioned having clinic days where mothers of pre-term or low-birth weight babies could come together and share their experiences, including KMC. Another health worker explained that at one point, they used to bring in mothers who had successfully done KMC to show others, but they feared this could spread infections to the babies and so stopped this.

> *Now just like you have invited us, we can also go out and teach other women who are not yet in the system (Mother, Bugiri group discussion)*
>
> *Even mothers that have practiced kangaroo should sensitize other people (Mother, Jinja district)*

Health Education and Training on KMC

Due to inadequate knowledge of KMC, mothers particularly recommended that pregnant mothers be taught during antenatal care about KMC, to avoid them having to hear of it for the first time when they had a pre-term birth. They also asked that husbands/partners/attendants be encouraged, for instance, through couple counseling to help them to do KMC. Health workers were supportive of teaching not only the mother but also those around her how to conduct KMC. Mothers and support persons also recommended raising awareness among communities, to sensitize them about KMC. They suggested different media, including radios, televisions, community meetings, posters in local languages for people to read, and integration of KMC into community outreaches on family planning. They said that this would in turn likely create more support among community members and reduce the burden of KMC being on the mother alone.

Several participants described the need to educate local council leaders for health and women and other political leaders about KMC and then have them as champions to support KMC programs and to encourage their communities to follow the advice of the health workers about KMC.

Training of more health workers on KMC was proposed by the health workers themselves. This included teaching all the relevant health workers KMC, including those not in SCUs, or providing refresher on-the-job training where needed. Many health workers were also supportive of having other cadres at health centers III and IV trained on KMC so that, where possible, they could provide it or initiate it and refer the baby in the KMC position.

DISCUSSION

This study set out to examine the barriers and facilitators to continuity of KMC at home following hospital discharge in rural Uganda. Results provide new insights into KMC practices at home in east-central Uganda, post-discharge, from the perspectives of a wide range of stakeholders across five districts. We have demonstrated that although key stakeholders including mothers, support persons, health workers, and other community leaders believe that KMC is important, practicing it is not always as simple or straightforward, especially after hospital discharge.

In all the facilities where the study was conducted, the mother–baby pair was discharged and expected to continue KMC at home. However, there was limited acknowledgment or preparation for how to maintain KMC within a setting very different from the closely monitored and regulated environment of the health facility. Many barriers that limit the consistent practice of KMC at home were described by study participants, for instance, lack of follow-up at home by health workers; the inability to quickly go back to the hospital in case of emergency; too many chores to do at home, often alone as per gender roles that diverted attention and time from doing KMC; financial challenges and reduced income; and inadequate knowledge; among others. These barriers resulted in less engagement with healthcare, KMC practiced less frequently, babies getting sick at home with parents unsure what to do next, high levels of psycho-social stress among mothers, and other adverse effects for mothers, babies, and the family.

Currently, there is a renewed global push to scale up KMC, including by WHO, which recently released results of a multi-country randomized controlled trial that reported the effectiveness of immediate KMC for small babies (2, 16). In Uganda, new guidelines for scale-up of KMC are under development. It is therefore a critical time to examine barriers and enablers of KMC practice following discharge from health facilities. It is important that the progress in improved infant survival and long-term health and developments that have been made through the implementation of KMC in hospitals are not lost after discharge. Indeed, many researchers have highlighted that community care must be linked to facility care in order to have successful KMC implementation (17–19).

Our study uniquely investigated and presented ideas for the improvement of KMC in the community from a range of key stakeholders. First, stakeholders recommended the provision of community follow-up by qualified health workers and CHWs. This recommendation is supported by previous research. Having a linkage and referral system between communities and providers via CHWs was identified as a potential enabler of KMC practice in Pakistan (1, 10, 20). In rural Malawi, a better follow-up of LBW babies after discharge was done through community follow-ups (21). An innovative CHW-led model of follow-up could be developed in Uganda, relying on the CHWs to do this monitoring, but with each CHW linked to a health facility or professional health workers whom they can contact for guidance. A blended workforce of health workers and CHWs may be needed to provide essential follow-ups for KMC support in the context of the human resource shortage in health that exists in Uganda and similar settings. However, this first requires that CHWs are taught about KMC practice, from initiation to danger signs and termination. Furthermore, funding is critical, for instance, to incentivize the CHWs in addition to thinking through how sustainability can be ensured.

Additionally, front-line, lower-level facility staff need to know about KMC so that they can either take part in the community outreach or more easily supervise it if CHWs are involved. The lower-level facilities are often more accessible to rural families, so if the baby needs a checkup or monitoring, they could be the first point of call before traveling to the hospital. This is also in line with our prior recommendations for newborn care to be strengthened at lower-level facilities (22).

Development of a peer-to-peer approach for KMC support would be complementary, with the mothers potentially more comfortable learning from other women with successful KMC stories, as recommended by the WHO (1). Peer-to-peer support in the community also potentially reduces the burden on the health workers and promotes knowledge transfer but may require some additional resources for sustainability. A systematic review identified enablers to KMC practice for caregivers, such as sharing positive testimonies of KMC by caregivers about its benefits; paternal involvement; peer support; trained nurses; and ability to do KMC at home (23).

Based on the findings from this study, we recommend advocacy and sensitization of communities about KMC and about care for small newborns with the goal of increased support for mothers and to enable families to continue KMC once back home, with fathers also encouraged to do KMC themselves. This could help reduce the stigma around pre-term and LBW babies and the expectations among many people that these babies will not survive. Families and communities should be educated about current survival and outcomes for pre-term and LBW newborns and the beneficial and harmful practices of caring for newborns, with emphasis on the necessity of abandoning dangerous practices like placing charcoal stoves in the same room as the baby. The use of charcoal stoves in the household has been linked to respiratory problems (24) and burn injuries (25). It appeared that KMC practice had not yet had enough impact on the eradication of harmful cultural practices. Communities must also be sensitized on the need to reduce the mother's workload once she is back home, as well as provision pf psycho-social support. They also need to be enlightened that KMC can be done by fathers as well as mothers.

Messages could be through traditional and social media, community meetings, posters in local languages, integrating KMC into community outreaches on family planning, among others. Local leaders should also be engaged to advocate for KMC programs. Similar strategies were successful in rural Malawi, with an integrated package of community-based sensitization interventions to reduce the stigma toward LBW babies (21). Further research will be needed to determine the effectiveness of these interventions in the Ugandan context, including determining the costs and acceptability of the interventions.

The strength of this study is that we provide experiences and perspectives from a wide variety of stakeholders/districts within a low-income setting. We also emphasize innovations suggested by the community members themselves through consensus, rather than by the researchers. We believe this could increase acceptability if these interventions are developed further. We were able to adapt the planned PLAs to meet the needs of the participants, especially since all mothers attended the group discussions with their babies, requiring adaptation of the activities into group discussions, with participants coming to a consensus on issues discussed.

CONCLUSION

We used a novel approach to engage diverse stakeholder groups to explore KMC uptake and sustainability in eastern Uganda. While global advocacy continues for increased uptake and scale-up of KMC, we need to be cognizant of other factors that play a role in its success, beyond the medical process and the mother's knowledge. We have also reported the required supporting factors for successful KMC practice in the community and innovations suggested by community members themselves.

Kangaroo mother care is not only a medical issue; it has sociocultural, economic, family, and community components too. There is a need for a holistic approach, including consideration of the baby's life and health after discharge, within the particular context of the mothers and families' social, economic, and psychological welfare. However, due to the financial implications, innovative use of locally available resources is needed. Importantly, KMC, including community KMC, should be integrated into routine health systems and newborn care to ensure better survival and optimal development of newborns.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Higher Degrees, Research and Ethics Committee at Makerere University School of Public Health and Uganda National Council for Science and Technology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DK, PWai, LF, and ES conceptualized the study design. DK, PWai, LF, ES, JI, and PWan contributed to the data collection, analysis, and drafting of the manuscript. All authors reviewed the manuscript and provided substantial input and approved the final manuscript.

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An outbreak of infection due to severe acute respiratory corona virus-2 in a neonatal unit from a low and middle income setting

Firdose Lambey Nakwa[1]*, Reenu Thomas[1], Alison van Kwawegen[1], Nandi Ntuli[1], Karabo Seake[1], Samantha Jane Kesting[1], Noela Holo Bertha Kamanga[1], Dikeledi Maureen Kgwadi[1], Neema Chami[1], Tshiamo Mogajane[1], Claude Ondongo-Ezhet[1], Thulisile Nelly Maphosa[1], Stephanie Jones[2], Vicky Lynne Baillie[2], Shabir Ahmed Madhi[2,3] and Sithembiso Velaphi[1]

[1]Department of Paediatrics and Child Health, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [2]South African Medical Research Council, Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [3]African Leadership in Vaccinology Expertise, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Introduction: The provision of kangaroo mother care (KMC) involving continuous skin-to-skin care (SSC) is an important intervention in neonatal care, which is recommended even when women are infected with severe acute respiratory syndrome coronavirus (SARS-CoV-2). We report on a nosocomial outbreak of SARS-CoV-2 infections in a KMC ward.

Methods: Contact tracing was conducted following the diagnosis of SARS-CoV-2 in a mother lodging in the KMC ward. All mother-newborn dyads in the KMC and healthcare workers (HCW) were tested for SARS-CoV-2 within 24–72 h of diagnosing the index case. Nasopharyngeal swab samples were obtained and tested from contacts, with a nucleic acid amplification test (NAAT) assay. Next-generation sequencing was done on positive samples. The secondary attack rate (SAR) was calculated assuming that the mother who presented with symptoms was the source of infection.

Results: Twelve (70.6%) of 17 mothers and 8 (42.1%) of 19 neonates who were in the KMC ward with the index case were found to be positive with SARS-CoV-2. Seven (87.5%) of the 8 neonates who tested positive had mothers who also tested positive. Seventy-five percent (9/12) of the mothers and 62.5% (5/8) of the neonates who tested positive were asymptomatic. Eight (27.6%) of 29 HCW were found to be positive and were all asymptomatic. One neonate died from *Acinetobacter baumannii* sepsis, and his post-mortem lung histopathology showed features compatible with SARS-CoV-2 pneumonia. The sequencing of 13 specimens, which included 1 mother-newborn dyad, indicated clustering to the same phylogenetic lineage with

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EDITED BY
Andrew Steenhoff,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
David Goldfarb,
University of British Columbia, Canada
Orkun Tolunay,
University of Health Sciences, Turkey
Jeffrey Pernica,
McMaster University, Canada

*CORRESPONDENCE
Firdose Lambey Nakwa
Firdose.Nakwa@wits.ac.za

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identical mutations. In assessing for factors contributing to this outbreak, it was found that spaces between beds were less than 1 m and mothers had their meals around the same table at the same time.

Conclusion: We report on a nosocomial outbreak of SARS-CoV-2 in a KMC ward, affecting a high number of mothers and neonates, and to a lesser extent HCWs. Although it is difficult to point to the index case as the source of this outbreak, as asymptomatic individuals can spread infection, the inadequate adherence to non-pharmaceutical interventions was assessed to have contributed to the spread of infection. This highlights the need for awareness and adherence to mitigation strategies to avoid SARS-CoV-2 outbreaks.

KEYWORDS

neonate, SARS-CoV-2, outbreak, langaroo mother care (KMC), non-pharmaceutical interventions (NPI)

Introduction

Respiratory droplets and aerosols are regarded as part of a continuum and represent the primary mode of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Smaller aerosol particles (<5 microns) may travel greater distances than the larger particles (>5 microns) and have been the mode of transmission in confined close contact spaces. A number of reports have shown a higher concentration of the SARS-CoV-2 closest to the infected or the presymptomatic index cases (1). Fomites, beds, computers, and bed rails have been identified as sources of transmission. Hospital areas frequented by medical staff had a higher yield of the virus than patient-accessible areas (1, 2). Hospital- or nosocomial-acquired severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been reported early in the course of the pandemic, with one South African hospital, where 6 clusters with 119 phylogenetically linked infections were identified, and 15 deaths were reported (3).

In a meta-analysis by Haley et al., the hospital-acquired secondary attack rate (SAR) varied from 0 to 17.1% with a pooled estimate of 3.6% (95% CI 1.0–6.9) and no difference between the patient population and the heathcare workers (HCWs). Household contacts had higher SAR than hospital-acquired infections. The SAR was highest in pre-symptomatic and symptomatic cases than in asymptomatic cases (4).

Neonates may be infected by SARS-CoV-2 rarely *via* vertical transmission *in utero* (5–7) and more commonly through airborne, droplet, and contact spread from their mothers and HCWs (8). In a recent systematic review, a pooled estimate of 3.2% of neonates born to women infected by SARS-CoV-2 at the time of delivery were infected during the perinatal period (9). A higher positivity rate in neonates has been reported in low- and middle-income countries (LMICs) at 5.1% compared to 3.8% in HIC (10). Thirteen percent of neonates tested positive in the INTERCOVID multinational study with data from 18 countries (11). Studies detailing pregnancy and neonatal outcomes are small case series and case reports. The small case series representing pooled data from LMICs such as Bangladesh, India, Nigeria, and Iran had reported a low positivity rate in neonates born to SARS-CoV-2 positive mothers (12–16).

Neonates may also be infected during community outbreaks or family cluster outbreaks (17–19). Nosocomial SARS-CoV-2 infection has been reported in adults (20), but there are few reports of nosocomial infections in neonates from LMIC (21–27). In national population studies in the United Kingdom and Spain, nosocomial-acquired cases were identified in 8/66 (12%) and 14/40 (35%) of positive neonates. The Spanish study was a prospective observational study in 79 hospitals with 26 community- and 14 nosocomial-acquired cases in neonates over an 8-week period. The median age at diagnosis in the nosocomial acquired cases was 14.5 (7.2–43 days) compared to 17 (11.5–26.5) days in the community-acquired cohort. The mothers and HCWs were considered to be possible sources of infection in 12 neonates (8). The United Kingdom study was a population-based study in SARS-CoV-2-positive neonates in the first 28 days over an 8-week period in 155 hospitals. Sixty-six neonates were positive, giving an incidence of 5.6%, with 17 neonates born to SARS-CoV-2-positive mothers and 8 neonates who had SARS-CoV-2 from the nosocomial transmission. Of these, 6 were preterm and acquired the infection >7 days after birth. The median age at diagnosis was 9.5 (7.5–11.0) days.

Half of the neonates who were SARS-CoV-2 positive had family members and close contacts who were also positive (28). Most of the neonates in both these studies were preterm with favorable outcomes and had neonatal comorbidities (8, 28).

In this report, we present findings of an outbreak of maternal and neonatal SARS-CoV-2 infections that occurred in a kangaroo mother care (KMC) ward in a public, tertiary hospital in a low- and middle-income setting.

Materials and methods

An investigation for SARS-CoV-2 infection of all mother-newborn dyads lodging in a 24-h KMC at Chris Hani Baragwanath Academic Hospital (CHBAH), and healthcare workers, was conducted after one of the women tested positive for SARS-CoV-2 infection following investigation for upper respiratory symptoms. CHBAH is a tertiary public hospital in Johannesburg, South Africa. It has a total of 3,200 beds, including a 185-bed neonatal unit consisting of 18 intensive care, 48 high care, 100 standard care, and 19 KMC beds. The daily bed occupancy is generally more than 80%.

The KMC ward is a facility for otherwise well preterm-born neonates who are awaiting weight gain, and their mothers are encouraged to lodge in the ward to offer skin-to-skin care (SSC) to their babies throughout the day. Neonates admitted to the KMC include those weighing between 1,000 and 1,700 g, not requiring supplemental oxygen or intravenous fluids, and whose mothers are available to room-in with the baby. Mothers provide SSC continuously on their beds except when bathing or having meals, during which the babies are placed in the bassinettes next to the mothers' bed. The ward accommodates up to 19 mother-neonate dyads.

The KMC ward is adjacent to another ward which is a standard care nursery (SCN) accommodating up to 20 neonatal admissions. Neonates admitted to SCN and KMC wards are assessed and managed by the same nursing and medical staff. Because of limited lodging facilities, women of neonates requiring hospital admission (sick and small neonates) not in the KMC ward were discharged home and could visit daily.

At the onset of the COVID-19 outbreak in South Africa, mothers were screened daily for symptoms suggestive of COVID-19 while staying in the KMC ward. On 8 June 2020, one of the mothers manifested a fever and cough and was diagnosed with COVID-19 following testing positive for SARS-CoV-2 from nasopharyngeal swabs, which was tested using a nucleic acid amplification assay test (NAAT). This mother was considered the index case for SARS-CoV-2 infection in this ward. She had been lodging in the KMC ward since 29 May 2020. She was counseled on self-monitoring and sent home to self-isolate.

Nasopharyngeal swabs were performed on all the other mothers and their babies who were residing in the KMC and investigated for SARS-CoV-2 using the NAAT assay, within 24 and 72 h after identifying the index case, respectively. The secondary attack rate (SAR) was calculated based on the probability of onward infection from an index case among a defined group of close contacts (4). Testing was also conducted on all the neonates admitted to the standard care nursery adjacent to the KMC. As part of the investigation, the specimens from mothers and babies that tested positive for SARS-CoV-2 on NAAT were sequenced by Next Generation Sequencing (NGS) at the Wits Vaccines and Infectious Diseases Analytics (Wits-VIDA) Research Unit. The cause of death attribution was undertaken by a multidisciplinary team including pediatricians, microbiologists, and pathologists, who evaluated the cause based on ante-mortem and post-mortem tests, including histology.

Testing for severe acute respiratory corona virus-2

Total nucleic acids were extracted from the respiratory swabs using the Bioer automated extraction system together with the MagaBio Plus virus DNA/RNA purification kit II as per manufacturers' instructions (Hangzhou Bioer Technology Co., Ltd, China). NAAT was performed using the U.S. Centers for Diseases Control and Prevention's emergency use authorization assays to detect SARS-CoV-2 (29). Samples were determined to be positive for SARS-CoV-2 when both of the nucleocapsid targets (N1 and N2) were positive with a cycle threshold (Ct) < 40. The samples were classified as inconclusive if only a single target was detected.

Genomic viral sequencing

Mothers and neonates who were tested SARS-CoV-2 PCR-positive underwent viral sequencing using Superscript IV with random hexamers (Life Technologies, Carlsbad, CA, United States) to generate cDNA. The Swift Biosciences' Normalase Amplicon and the SARS-CoV-2 amplicon panel (30) were used to amplify and index paired-end libraries of the genomic DNA. The resulting libraries were sequenced using a 300 cycle v2 MiSeq Reagent Kit on an Illumina MiSeq instrument (Illumina, San Diego, CA, United States).

Genome assembly and phylogenetic analysis

The Genome Detective 1.126 and the Coronavirus Typing Tool[1] were used to generate paired-end fastq reads (31). The bcftools 1.7-2 mpileup method was then used to filter out the low-quality mutations, and all the sequences were deposited

1 https://www.genomedetective.com

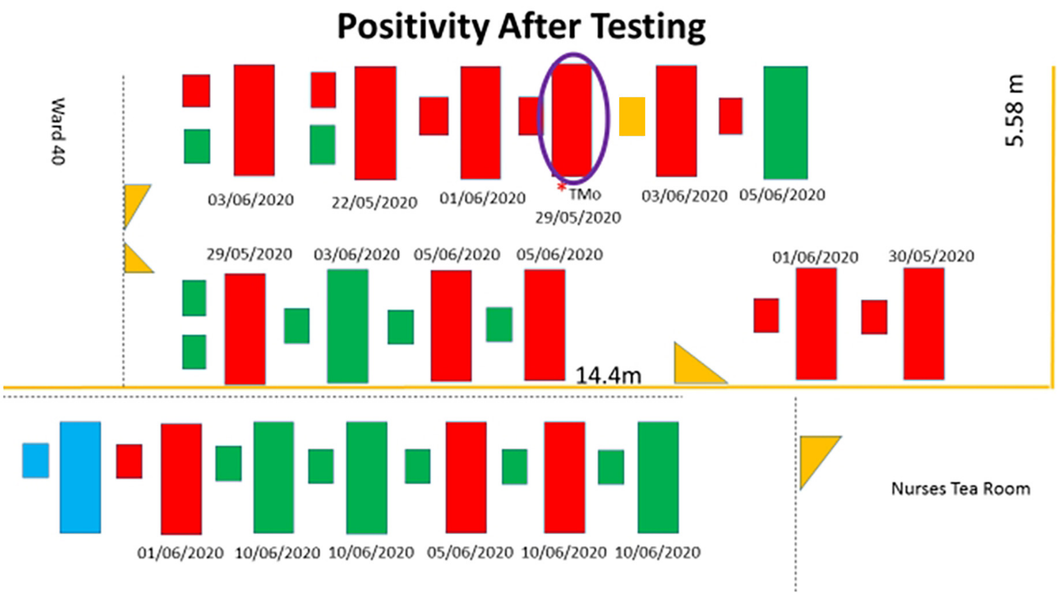

FIGURE 1
Schematic representation with the mothers and neonates who tested positive shaded in red. The beds shaded in green are mothers and neonates who tested negative, and the beds shaded in blue are not occupied. The large rectangle represents the maternal beds, the smaller rectangles adjacent to the large rectangles represent neonatal beds, and two smaller rectangles represent a set of twins. The purple circle represents the index case. The small orange rectangle represents the neonate who was not tested. Yellow triangles are doors. The dates below the beds are the dates of admission to the KMC ward.

in GISAID.[2] A custom pipeline based on a local version of NextStrain was used for the phylogenetic analysis using a South African dataset with genomes collected during the same time as the study period. Genomes with low sequence genome coverage (<90%) were filtered out of the pipeline which contains several python scripts that manage the analysis workflow. It performs alignment of genotypes in MAFFT, phylogenetic tree inference in IQ-Tree20, ancestral state construction, and annotation.[3]

Data analysis

The medical records of all the mothers and neonates who were tested and had NAAT results available were reviewed for clinical characteristics and outcomes at hospital discharge. The proportion of mothers and neonates with positive SARS-CoV-2 results, including the concordance of SARS-CoV-2 results between neonates and their mothers, and between twins were assessed.

The clinical and laboratory data were collected prospectively and information on outcomes was extracted from the medical records. Descriptive stats were represented as numbers and proportions.

2 https://www.gisaid.org/
3 https://github.com/nextstrain/ncov

Ethics approval

Permission to report on this outbreak was acquired from the hospital management, and ethics approval was obtained from the University of the Witwatersrand Human Ethics Research Committee (Protocol Number – M200505).

Results

There were 17 mothers and 20 babies (including 3 sets of twins) admitted in the KMC ward between 8 June 2020, the day the index case was investigated, and 10 June 2020 when her SARS-CoV-2 result was received. Thirteen (76%) mothers had been admitted to the ward since 29 May 2020 and four (24%) were admitted between 8 and 10 June 2020. The bed location of mother-newborn dyads who were tested following confirmation of COVID-19 in the index case is presented in Figure 1. All infants were born preterm (<36 weeks), with median birth weights of 992.5 (750–1,600) g, and the median weights at the time of the test were between 1562.5 (1470–1640) g. The median postnatal age at the time of testing was 50.5 (23–72) days. Respiratory distress syndrome was the admitting diagnosis to the neonatal unit at birth for all the neonates who were positive for SARS-CoV-2. One neonate who had underlying chronic lung disease (CLD) was weaned to room air before admission to the KMC ward. This neonate decompensated

TABLE 1 Results of COVID test and outcome of the mothers and neonates in the kangaroo mother care (KMC) ward.

COVID-19 result	Baby result	Outcome
Positive	Positive	Discharged
Positive	Positive	Discharged
Negative	Positive	Demised
Negative	Negative	Discharged
Positive	T1 Negative/T2 Positive	Discharged/discharged
Positive	T1 Positive/T2 Negative	Discharged/discharged
Positive	Negative	Discharged
Positive	Negative	Discharged
Positive	Not tested	Discharged
Positive	Positive	Discharged
Positive	Positive	Discharged
Positive	Positive	Discharged
Positive	Negative	Discharged
Positive	T1 Negative/T1 Negative	Discharged/Discharged
Negative	Negative	Discharged
Positive	Negative	Discharged
Negative	Negative	Discharged
Negative	Negative	Discharged

and required ventilation and subsequently demised after being infected by SARS CoV-2.

Twelve (70.6%) of 17 mothers and 8 (40%) of 20 neonates (including neonates of the index case) tested positive for SARS-CoV-2 infection (**Table 1**). One neonate was discharged and taken home by the mother after she was tested (she tested positive), but before her infant could be tested. Seven (87.5%) of the eight positive neonates had mothers who tested positive. Of the 12 neonates, including a set of twins, who tested negative for SARS-CoV-2, 6 (50%) of these mothers were infected with SARS-CoV-2. Overall, 20 of the 36 neonates tested after the index case was identified, were positive. If one assumes that the source of infection was the index case and considering the mother and infant as independent individuals, the overall secondary attack rate was 55.5% (20/36), and when mother-infant dyads are considered as one individual, the transmission rate was 76.5% (13/17).

All the three mothers who had twins were positive for SARS-CoV-2, but only one of two sets tested positive, and both neonates of the third set of twins were negative (**Table 1**).

Outcomes of severe acute respiratory corona virus-2-positive mothers and infants

Among the 12 women who tested positive and confirmed to be infected by SARS-CoV-2, nine (75%) were asymptomatic, and three had mild upper respiratory tract symptoms. All the women infected with SARS-CoV-2 were discharged upon diagnosis for self-isolation at home, and one was sent to a government isolation facility.

Three (37.5%) of the neonates who had a reactive NAAT test were symptomatic. There was a single death in one of the neonates with COVID-19 who developed nosocomial pneumonia and warranted mechanical ventilation and cultured multi-drug resistant *Acinetobacter baumannii* in blood. Post-mortem histopathological findings (13 days after the SARS-CoV-2 positive result), obtained by targeted minimal invasive tissue sampling, revealed hyaline membrane, type II pneumocyte proliferation, interstitial inflammation, markedly reactive bronchial cells, and intravascular thrombi, which could be consistent with COVID-19. The immediate cause of death was assigned to be attributed to *A. baumannii* nosocomial sepsis with the antecedent cause related to nosocomial SARS-CoV-2 and acute respiratory distress syndrome due to SARS-CoV-2 (32).

There were 13 babies in the adjacent SCN ward who were also tested, all of whom had a non-reactive NAAT for SARS-CoV-2. One of these neonates was tested positive on a subsequent visit to the pediatric casualty ward 10 days after having been discharged on 15 June 2020, and this neonate was declared to be deceased upon arrival at the hospital. The verbal autopsy revealed that the neonate had difficulty with breathing on the evening of 24 June 2020 and was taken to the family physician who sent the neonate home on unspecified treatment. The baby was noted to be unresponsive in the early hours of the morning of 25 June 2020 and brought to the hospital.

The next-generation sequencing was successfully performed in samples from 10 (77%) of 13 women and 3 (38%) of 8 neonates, with the remaining samples not sequenced due to low viral loads (cycle threshold >32). The sequenced samples included one mother-newborn dyad. All of the genomes were of the C.35 PANGO lineage classification; furthermore, all of the genomes clustered very closely together during the phylogenetic analysis with identical mutations at D614G and P314L positions (**Figure 2**). A single genome from one neonate clustered with the other outbreak genomes, albeit having several additional mutations at A831V.

Twenty-nine healthcare workers (3 doctors, 25 nurses, and 1 ward clerk) who worked in the KMC ward were also tested for SARS-CoV-2 as part of the outbreak investigation; 27.6% (8/29; 1 doctor, 6 nurses, and 1 ward clerk) had a reactive SARS-CoV-2 NAAT.

On reviewing the activities in the ward, it was identified that the mothers shared the same table for meals without observing social distancing. The mothers had been wearing cloth face masks during their stay in the ward. During the assessment of spacing between beds, the distance between the edges of the beds for mothers was recorded as 75 cm and between baby and mother was recorded as 25 cm.

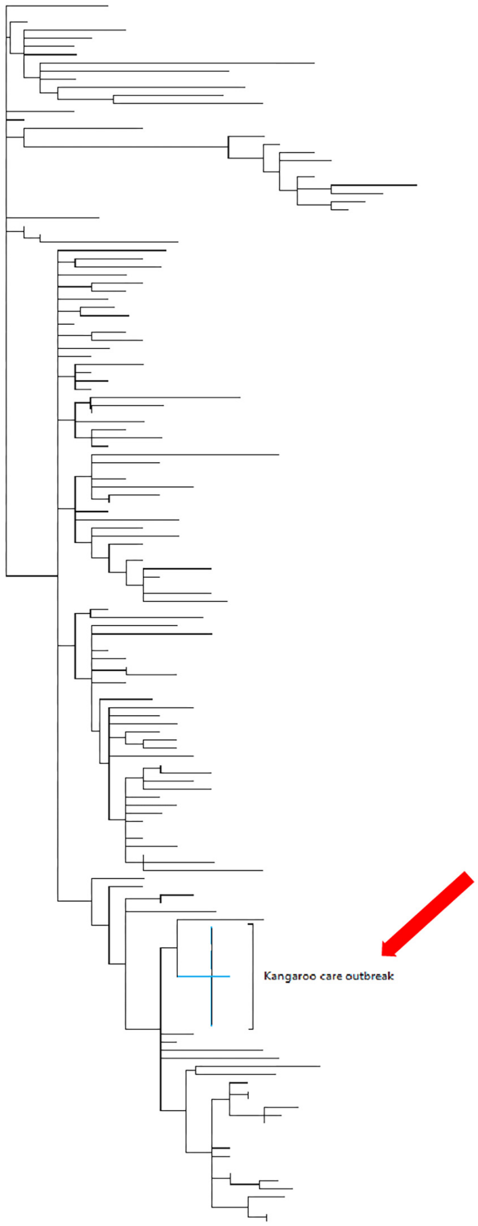

FIGURE 2
The maximum clade credibility phylogeny of the mother and babies who tested positive during the outbreak in the Kangaroo care ward. Phylogenetic tree of 160 genomes collected in SA during the time that the outbreak had occurred. The maximum clade credibility phylogeny of the mothers and neonates who were tested during the outbreak in the KMC ward (red arrow). This indicates that the genomic data obtained from the 10 mothers and 3 neonates were clustered closely together.

Discussion

We report on a nosocomial outbreak of SARS-CoV-2 in a KMC ward, affecting mothers and their infants. Forty percent of neonates and 70% of mothers in the KMC ward were positive during this outbreak and 27.6% of HCWs were found to be positive. Other than the index cases, most mothers and infants who tested positive were asymptomatic. Vertical transmission was considered to be unlikely as the babies in the KMC ward were chronologically older, thus, more likely to be a horizontal transmission.

A number of studies have reported on the mother-to-infant transmission of SARS-CoV-2 but most of them were around the time of birth or soon after birth, and they reported low transmission rates of less than 3.2% (9). A more recent meta-analysis reported a higher transmission rate of 12% in a study where 54 neonates were positive for SARS-CoV-2. Most of these studies reported that infants were placed 6 ft or 1.5 m from their mothers and offered intermittent SSC, but they did not report on the duration of SSC (7, 33–36). A national study from India had 21 (1.43%) neonates who tested positive beyond 72 h and reported these as horizontal transmission and had a higher positivity rate in neonates rooming in with their mothers (22). Being in a ward where there is a documented SARS-CoV-2 outbreak and documented contact with a suspected SARS-CoV-2 patient have been reported as risk factors for nosocomial SARS-CoV-2 infections (37). The rates of infection were also noted to be higher if the duration of exposure was for longer than 5 days (4). In this study, where continuous SSC was a norm, there was a high mother-to-child postnatal transmission rate or concordance rate. While the inadequate implementation of NPI most likely contributed to the spread of infection and hence the higher transmission rate, it is possible that a continuous provision of SSC by a SARS-CoV-2-positive mother increased the risk of transmission compared to intermittent SSC.

Many studies have reported low or no mortality in neonates infected by SARS-CoV-2. In this study, we report that one (12.5%) of the neonates who were positive subsequent to this outbreak died with features suggestive of SARS-CoV-2, though the immediate cause was assessed to be healthcare-associated infection due to *A. baumannii*. In reviewing this death, the histopathological changes observed were not in keeping with *A. baumannii* sepsis. The second neonate who died was in the SCN during the time of this outbreak. Though he was negative at discharge, it is possible that he acquired the infection during this outbreak as he presented within 14 days of the outbreak, but the acquisition of infection from the home or community cannot be excluded.

All the specimens sent for next-generation sequencing had the same lineage classification, and the genome of each specimen was clustered closely together on the phylogenetic tree. Thus, there was a common source for the outbreak in the KMC ward. These were representative of the common SARS-CoV-2 PANGO lineages circulating during the pandemic (38). Healthcare worker specimens were analyzed by a different laboratory and hence were not sent for NGS. Therefore, we could not conclusively state that a healthcare worker from the community was the primary source.

The response to the outbreak was to increase the space between beds from 75 to 150 cm. Mothers were offered surgical masks to wear at all times and were divided into two groups when going for meals to allow a space of 150 cm between mothers during meals. Mothers who came from home were screened for symptoms and tested for SARS-CoV-2, and only those who tested negative were admitted in the 24-h KMC ward. The positive mothers were only accepted into the KMC ward to perform 24-h KMC after they had completed 10 days of isolation at home or in a government isolation facility. There have been no other cases of COVID-19 from the KMC ward since the implementation of the above measures.

Limitations of the study are that we did not swab the environment, the beds, bed rails, bedside lockers, or any of the ablution facilities or the staff common areas. Environmental swabs and airborne samples were not taken to investigate for SARS-CoV-2. The HCW nasopharyngeal swabs were not sent for NGS testing as these were tested by a different laboratory and we had no access to these samples. Strengths are that it reports on an outbreak in a KMC ward and the importance of NPI measures and screening.

Our recommendations are that all mothers coming for labor and delivery should be screened and/or tested for SARS-CoV-2. Mothers who tested positive should be isolated, and those whose babies are well, to room-in with their babies and provide intermittent SSC during breastfeeding, keeping the 1-m distance between baby and mother in between feeds, mothers should wear surgical masks, especially during breastfeeding and practice hand hygiene. The mothers who test positive and are to remain in hospital to provide continuous SSC in the KMC ward with other negative mothers, these positive mothers to only be admitted to the KMC ward after 10 days of isolation. For mothers whose infants might have been too sick or too small for them to lodge while waiting for their infants and therefore were sent home, they must be screened for symptoms and tested for SARS-CoV-2 before readmission to the lodger facility or KMC ward. Mothers who are symptomatic and/or test positive should not be admitted to KMC; they should be referred to their family doctor or physician depending on the severity of symptoms and to be in isolation or quarantine. They should be readmitted once they have been discharged by their physicians or are de-isolated. Mothers should be encouraged to express breastmilk and ask the family members to bring the breastmilk to the hospital for the baby.

Conclusion

This study reports on a SARS-CoV-2 outbreak in a KMC ward with mothers, neonates, and HCWs infected. The majority of the infected neonates had a good outcome in terms of respiratory morbidity. There was a low mortality rate. The outbreak highlights the importance of adhering to NPI in mitigating the spread of SARS-CoV-2 in a hospital setting with such close and prolonged contact. As we aim for zero separation of mother–newborn dyads and promote rooming-in and breastfeeding, even in mothers who are infected with SARS-CoV-2, we must impress on strategies to curtail the spread of these infections.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The data presented in the study are deposited in the GISAID EpiCoV repository and the accession numbers are: EPI_ISL_12690551, EPI_ISL_12690550, EPI_ISL_12690542, EPI_ISL_12690553, EPI_ISL_12690541, EPI_ISL_12690552, EPI_ISL_12690544, EPI_ISL_12690555, EPI_ISL_12690543, EPI_ISL_12690554, EPI_ISL_12690546, EPI_ISL_12690557, EPI_ISL_12690545, EPI_ISL_12690556, EPI_ISL_12690548, EPI_ISL_12690547, and EPI_ISL_12690549.

Ethics statement

The studies involving human participants were reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

FN and SV conceptualized and analyzed the data of the study and wrote the first draft. FN, RT, AK, NN, SK, KS, NK, DK, TNM, CO-E, TM, and NC collected and analyzed data. VB, SJ, and SM analyzed and interpreted the NGS data. All authors analyzed the drafts and are accountable for the content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Andrew Steenhoff,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Peter Cooper,
University of the Witwatersrand,
South Africa
Kwabena Osman,
University of Ghana, Ghana

*CORRESPONDENCE
Anna B. Hedstrom
hedstrom@uw.edu

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Respiratory distress syndrome management in resource limited settings—Current evidence and opportunities in 2022

Osayame A. Ekhaguere[1], Ikechukwu R. Okonkwo[2], Maneesh Batra[3] and Anna B. Hedstrom[3]*

[1]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States, [2]Department of Pediatrics, University of Benin Teaching Hospital, Benin City, Nigeria, [3]Departments of Pediatrics and Global Health, University of Washington, Seattle, WA, United States

The complications of prematurity are the leading cause of neonatal mortality worldwide, with the highest burden in the low- and middle-income countries of South Asia and Sub-Saharan Africa. A major driver of this prematurity-related neonatal mortality is respiratory distress syndrome due to immature lungs and surfactant deficiency. The World Health Organization's Every Newborn Action Plan target is for 80% of districts to have resources available to care for small and sick newborns, including premature infants with respiratory distress syndrome. Evidence-based interventions for respiratory distress syndrome management exist for the peripartum, delivery and neonatal intensive care period- however, cost, resources, and infrastructure limit their availability in low- and middle-income countries. Existing research and implementation gaps include the safe use of antenatal corticosteroid in non-tertiary settings, establishing emergency transportation services from low to high level care facilities, optimized delivery room resuscitation, provision of affordable caffeine and surfactant as well as implementing non-traditional methods of surfactant administration. There is also a need to optimize affordable continuous positive airway pressure devices able to blend oxygen, provide humidity and deliver reliable pressure. If the high prematurity-related neonatal mortality experienced in low- and middle-income countries is to be mitigated, a concerted effort by researchers, implementers and policy developers is required to address these key modalities.

KEYWORDS

respiratory distress syndrome (RDS), low- and middle-income countries, treatment, surfactant, continuous positive airway pressure (CPAP), low resource, prematurity

Background

Childhood mortality is predominantly driven by deaths in the neonatal period (the first 28 days of life) (1). In the last 30 years, reductions in neonatal mortality have not kept pace with those beyond the first month of life (1). Consequently, 47% or an estimated 2.4 million of all childhood deaths occur in the newborn period, with births occurring before 32 weeks gestation carrying the highest risk of death (2, 3).

To focus the world's attention on needed improvements to close this gap, the Sustainable Development Goals revised targets in 2015 to reduce neonatal mortality to 12 per 1,000 live births by 2030 (4). The Every Newborn Action Plan (ENAP) identified the management of the complications of prematurity as a high-yield area for improvement critical to reducing neonatal deaths (2, 5).

Between and within-country variation in premature birth rates and prematurity-related mortality exist, with low- and middle-income countries (LMIC) carrying the highest burden (6). Over 90% of extremely preterm babies (<28 weeks) born in LMICs die within the first few days of life, while <10% of extremely preterm babies die in high-income countries (HICs) (6). Improving access to facilities capable of delivering quality neonatal care for small and sick newborns has been identified as a target of the ENAP (5). Specifically, the ENAP coverage target has called out the goal of having 80% of districts with available care for small and sick newborns (7). World Health Organization (WHO) guidelines on transforming care for small and sick newborns target key treatment modalities (Figure 1) for primary health facilities including neonatal resuscitation; secondary facilities including oxygen, continuous positive airway pressure and methylxanthines; and in addition to these, for tertiary facilities surfactant and mechanical ventilation (8).

The drivers of prematurity related mortality are multifaceted and related to the immature organ-systems of the preterm newborn. However, respiratory distress syndrome (RDS), which results from lung immaturity and surfactant deficiency, contributes about 45% of case-fatality due to prematurity in LMICs (9). Risk of RDS associated mortality is inversely related to the degree of prematurity. Given its contribution to prematurity-specific mortality, optimizing and scaling RDS specific interventions is paramount for reducing neonatal mortality at a population level, as is targeted by ENAP. In this paper, we review the pathophysiology of RDS, review RDS-specific interventions including their mode of action, available evidence that supports their use in High and LMICs and discuss research and operational gaps that exist which are specific to LMICs.

Respiratory distress syndrome

The development of RDS begins with impaired or delayed surfactant synthesis and secretion in the immature lung. Between 24 to 28 weeks of gestation, type II alveolar epithelial cells begin production of surfactant, however, this innate surfactant production is often insufficient for extra-uterine life until after 35 weeks (10). The primary function of surfactant is to reduce the surface tension of the air-liquid interface in the alveoli. When deficient, atelectasis, ventilation-perfusion mismatch, and hypoventilation ensues with resultant hypoxemia, hypercarbia, and impaired endothelial and epithelial integrity with leakage of proteinaceous exudate and formation of hyaline membranes and injury to the immature lung (11). Perinatal risk factors for developing RDS include lower gestational age and birth weight, male sex, cesarean delivery without labor, maternal diabetes, and perinatal hypoxic-ischemic events (11–13). In contrast, antenatal steroids, hypertensive disorders in pregnancy, and prolonged rupture of membranes are perinatal factors associated with a reduced risk of developing RDS (12, 14). Certain postnatal conditions including acidosis, hypothermia, hyperoxia, poor perfusion, baro and volutrauma from assisted ventilation, affect surfactant production, function, and metabolism (11).

The incidence of RDS is inversely related to gestational age. It occurs in 98% of preterm infants between 22 and 24 weeks gestation but only 25% of those with birth weight between 1,251 to 1,500 grams (15, 16). The signs of RDS are non-specific, and not all preterm infants below 34 weeks gestation presenting with respiratory distress have RDS. Examples of conditions that can mimic RDS include retained lung fluid, meconium aspiration syndrome, persistent pulmonary hypertension, and pulmonary hypoplasia (11, 17). RDS, however, clinically worsens in the first few days after birth hence, early diagnosis is important to ensure prompt treatment and transfer as necessary. RDS can increase the risk of pneumothorax and in severe cases, or where appropriate therapy is not available, can lead to respiratory failure and death (17).

Diagnostic challenges

In HICs, RDS is diagnosed in preterm infants who have signs including supraclavicular, intercostal, and subcostal retraction, grunting and flaring of the nares, requirement for supplemental oxygen as dictated by hypoxia from pulse oximetry, and have chest radiographic findings of diffuse haziness and air bronchograms (18). Additionally, blood gas analysis to assess for acidosis, hypoxemia, and hypercapnia may be included in the diagnostic criteria. These parameters are also used to determine the need for the initiation or escalation of respiratory support.

However, the use of chest radiographs, pulse oximetry and blood gas analysis are resource intensive and not commonly available in LRS. Hence, the most feasible assessments for RDS in LRS include objective criteria for assessing work of breathing, such as scoring systems that are simple, non-invasive, inexpensive and have shown both prognostic value and good inter-rater-reliability. Most commonly in use are the Downes score and the Silverman Andersen Respiratory Severity Score (19, 20). In one study among nurses trained to use the Silverman Andersen Score, the intra-class correlation coefficient was 0.88 (CI 0.72–0.98) (21). Similarly, in another study among nurses trained to use the Downes score reported an inter rater reliability of 0.71 (22). These scores assess work of breathing specific to the physiology of newborns such as chest wall flexibility and use of accessory respiratory muscles. Components of these

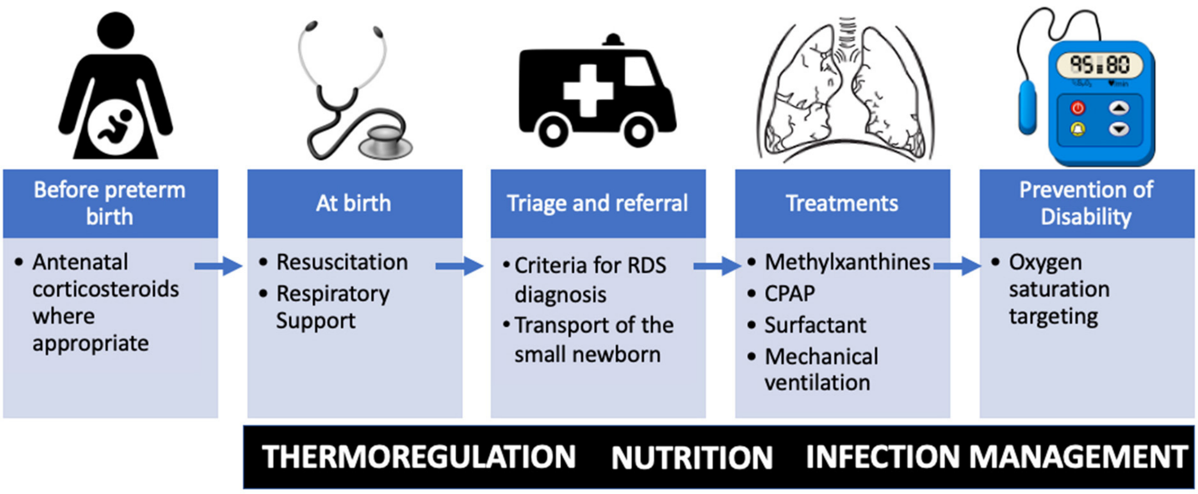

FIGURE 1
Essential therapies for respiratory distress syndrome (RDS) in resource limited settings along the time course of preterm birth. Important fundamental premature care includes thermoregulation, nutrition, and management of infection. CPAP, continuous positive airway pressure.

scores include exam findings of work of breathing, cyanosis, and degree of tachypnea (Figure 2). Neonates are scored on each component from 0 to 2 and their total score is from 0 to 10, where 10 represents severe distress. Elevated scores correlate to an increased likelihood of requiring advanced respiratory support (23, 24). Silverman Andersen score in the 4–6 range is commonly used as a threshold for initiation, and titration of CPAP therapy given it can be serially repeated at the bedside as a type of vital sign (23, 25).

Antenatal corticosteroids

In the 1960s, animal studies showed corticosteroids accelerated lung maturation (26). In subsequent human trials, antenatal corticosteroid (ACS) given to the pregnant woman prior to preterm birth improved survival in premature infants primarily by reducing RDS incidence (14). Consequently, ACS became the standard of care in pregnancies between 24 0/7 weeks and 33 6/7 weeks of gestation at risk of delivery within 7 days (27–29). In high-income settings, over 80% of at-risk pregnancies receive ACS (30, 31). However, its use in low resource settings remains low and sporadic (32). Betamethasone is most commonly used in HIC, however, it is not readily available in LRS (33). Hence, WHO has recommended the use of dexamethasone as a substitute to betamethasone (27). Evidence suggests both betamethasone and dexamethasone are equivalent in the effect (34, 35).

Informed by models and strong evidence from both high, and upper middle-income countries that suggested ACS may prevent prematurity-related neonatal mortality (36–38), the National Institutes of Child Health and Human Development sponsored the population-based ACS cluster-randomized trial (39). This trial was conducted in peri-urban and rural settings in geographical clusters in Argentina, Guatemala, India, Kenya, Pakistan and Zambia (39). Women assessed to have signs of preterm labor, preterm premature rupture of membranes, pre-eclampsia or eclampsia, or obstetric hemorrhage were included. The primary outcome was 28-day neonatal mortality among infants less than the 5th percentile for birthweight—a proxy for preterm birth as gestational age could not be reliably determined (39). The proportion of infants with birth weight <5th percentile was 5% (2,362/48,219) and 4% (2,094/51,523) in the intervention and control group, respectively. The results of this trial showed no benefit on mortality in neonates with birth weights <5th percentile, increased risk of mortality in neonates >2,500 g, and an increased incidence of maternal infection (39). Notable variations in the study outcome occurred by study region. Among African sites included in the trial, ACS was associated with increased risk of mortality among neonates with birth weights <5th percentile (39). Further sub-regional analysis to evaluate why better outcomes were observed in some regions and not others, suggested for example, that better obstetric and neonatal care may have been associated with the improved outcomes observed in Guatemala (40).

After this study, the WHO issued guarded recommendations for ACS to be used in health facilities capable of assessing gestational age, diagnosing maternal infection, and providing emergent obstetric and preterm neonatal care, including resuscitation, respiratory, thermal, and nutritional support (27). Subsequently, the Antenatal Corticosteroids for Improving

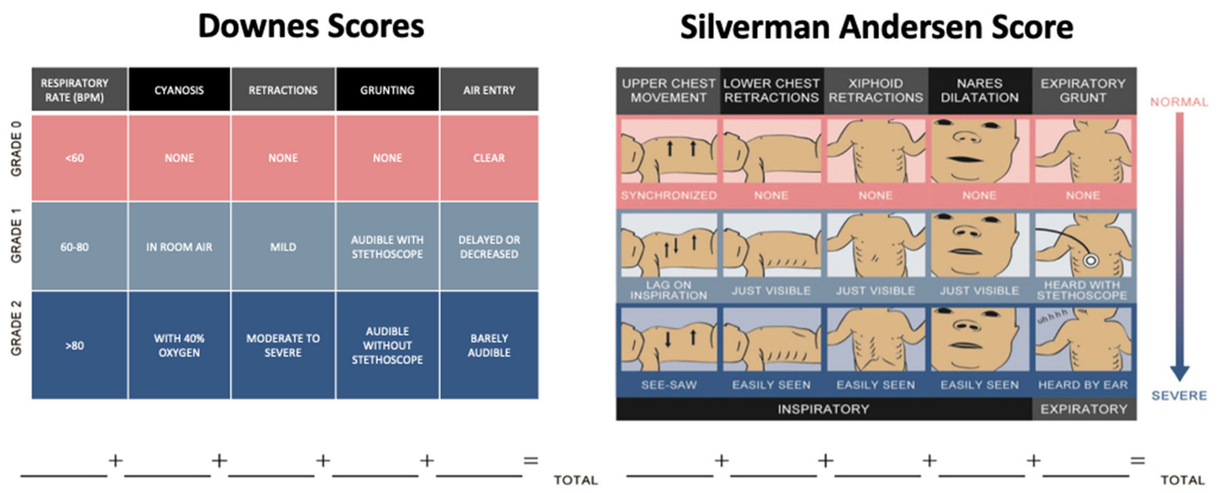

FIGURE 2
Scoring systems for respiratory distress syndrome. Downes and Silverman Andersen scores assign 0–2 points for each of five categories of respiratory distress (19, 20). Part of figure reprinted with permission from (25).

Outcomes in preterm Newborns (ACTION-1) Trial-sponsored by the WHO-randomized pregnant women between 26 0/7 weeks and 33 6/7 weeks of gestation at centers capable of gestational age assessment, who were at risk for preterm birth to either dexamethasone or placebo. This trial showed ACS resulted in a 16% and 12% risk reduction in neonatal mortality and stillbirths (41). To evaluate the impact of ACS on late preterm infants or those >2,500 g, the ACTION-2 trial was conducted in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who were at risk of preterm labor (42). The results from the ACTION-2 trial, showed ACS did not increase the risk of mortality and reduced the need for resuscitation by 62% (42).

Taken together, these trials on ACS among pregnant women in LMICs at risk of preterm delivery indicate that with close monitoring and the provision of neonatal interventions for preterm newborns, ACS has the potential to substantially reduce prematurity-related mortality. However, a significant proportion of deliveries in LMICs still occur in resource limited settings where the quality of care required to reap the benefits of ACS may be unavailable. Research on how to effectively monitor women at risk of preterm delivery, optimize neonatal resuscitation and increase availability of level two newborn care including respiratory support with limited resources as recommended by WHO is required. Also, investments and research into optimizing the referral and safe transportation systems to higher-level facilities for the at-risk mother, would increase access to ACS.

Transport of the small and sick newborn

While desirable, *in utero* transfer of pregnancies at risk for preterm delivery to a center capable of providing high-quality obstetric and neonatal care is not always feasible (43, 44). WHO recommends small or sick newborns receive a timely referral through integrated newborn service pathways with continuity of care, including during transport (45). In high resource countries the practice of inter-healthcare facility transportation of critically ill neonates continues to expand and has evolved into mobile ICUs capable of delivering state-of-the-art critical care outside the NICU, thus maintaining or improving the continuum of care (46). Anticipating the need for transfer early, appropriate preparation for transfer, and ongoing high-quality care during transfer, are the cornerstones of quality neonatal transport systems (44). Maintaining early supportive care is especially important for the treatment of RDS including use of oxygen and CPAP. However, the availability and quality of referral systems in LMICs are limited (47). In a study from Nigeria that examined 411 neonatal transports, no referral information was available upon presentation to the tertiary referral center. In that study, only 4% arrived by ambulance, 0.7% in a transport incubator, and 7% were accompanied by a health professional (48). This pattern is common in most published observational studies from other countries as well (47, 49). Of the few studies from South Africa where medical services are more established, limitations in availability of resources and effective communication between facilities were limitations of the transport systems (46, 50).

Safe and timely inter-facility transport of small and sick newborn infants including those with RDS is critical to maintain the continuum of care from the referring to the referral hospital. National commitments, investments, and research into optimizing and examining the effect of inter-facility transport on neonatal mortality are critical for further improvements in prematurity-related mortality and morbidity.

Delivery room management

Initial respiratory support for some premature infants with RDS requires careful bag mask ventilation to establish lung functional residual capacity. In anticipation of a preterm delivery, appropriate preparation includes availability of a working self-inflating bag and appropriately sized facemask, as well as an emergently available provider trained in resuscitation to focus on the newborn. Helping Babies Breath is a low cost, well established program to train providers to perform these key interventions (5, 51, 52). Implementation of this program has been shown to reduce intrapartum-related stillbirths and 1-day neonatal mortality rate (53). Challenges for scale up of HBB, however, include limited time for training, retention of trained staff, and learners subsequently translating simulation skills into consistent behavioral change (54). Research suggests low dose, high frequency refresher strategies are associated with best retention (54). While the HBB program addresses resuscitation for the majority of births globally, the program is not targeted toward care of the preterm infant.

Tertiary facilities in LMIC may have greater capacity for resuscitation of the premature newborn than what is presented in HBB. Where resources allow, use of the Neonatal Resuscitation Program provides additional training for the initial management of preterm newborns, such as emergent endotracheal intubation and continuous positive airway pressure (CPAP) (55).

The Neonatal Resuscitation Program recommends the use of CPAP when respiratory distress persists after initial resuscitation despite establishment of a normal heart rate and spontaneous respiration (55). This use of CPAP shortly after delivery reduces the risk of subsequent intubation, surfactant use, and ventilator days and is a useful therapy where equipment and expertise are available. CPAP use among preterm infants does increase the risk of pneumothorax, so should be used with caution, and where availability of staff and resources to manage this complication are available (56–59).

Continuous positive airway pressure

The primary consequence of RDS (surfactant deficiency) is alveolar collapse and the loss of functional residual capacity. In spontaneously breathing infants with RDS, CPAP provides continuous distending pressure to the airway and lungs (45, 60). This pressure provides the driving force to overcome the elastic, flow-resistive, and inertial resistance of the respiratory system and restore functional residual capacity (61). The continuous pressure applied *via* a nasal interface enhances lung inflation, decreases work of breathing and is associated with decreased mortality due to RDS (60, 62). CPAP also decreases the risk of chronic lung disease, one of the major sequelae of RDS that often requires the baby receive pulmonary care up to or beyond term-corrected age (63).

CPAP devices can be grouped into two broad categories based on the method of pressure generation. Devices that use an adaptive flip valve located at the nasal interface to generate CPAP are termed variable flow devices (64). Devices that generate pressure by preventing gas egress from the circuit, because of an expiratory limb resistance or a titratable PEEP valve, are termed continuous flow devices (64). One form of continuous flow CPAP device is one where the expiratory limb is submerged in liquid with the depth of insertion coinciding with the pressure in the circuit. These "bubble CPAP" devices result in less failure of CPAP and can be generally made at a lower cost than other forms of CPAP (65). Most CPAP devices available in HIC are expensive, ranging from US$2000 to US$6000—not including the cost of consumables (66, 67).

Evidence from HIC suggest that compared to supplemental oxygen, the use of CPAP is an effective treatment for preterm infants with RDS (68). A 2020 Cochrane systematic review of CPAP vs. supplemental oxygen and the effect on treatment failure and death included five studies and 322 preterm infants with RDS from HICs. In this review, treatment with CPAP significantly lowered the risk of death, or use of mechanical ventilation [typical risk ratio (RR) 0.64, 95% confidence interval (CI) 0.50 to 0.82; typical risk difference (RD) −0.19, 95% CI −0.28 to −0.09] (68).

The cost of CPAP devices, unavailability of consumables and spare parts, maintenance needs, and dependence on electricity have limited the availability and use of commercialized CPAP devices in LMICs (67, 69). To fill this gap, multiple low-cost CPAP devices have emerged ranging from those crafted locally by providers at the bedside, to lower-cost commercialized devices (70–81). In comparison with commercial device available in HIC settings, the improvised devices lack some features raising questions regarding their efficacy and safety (72, 82–84). Specifically, the improvised devices often lack heated humidity relying only ambient humidity. The available tubing in low resource settings for assembly of CPAP are for standard nasal cannula which are of narrower bore than those typically used with commercialized CPAP circuits (85). The nasal cannula interface used are also not specifically designed to transmit pressure from CPAP and may attenuate the delivered pressure (85–87). Despite the lack of available reliable CPAP devices, a systematic review of 21 observational quasi randomized and observational studies using improvised CPAP devices concluded

TABLE 1 Features from the UNICEF target product profile for neonatal continuous positive airway pressure for use in low- and middle-income countries (88).

Characteristic	Optimal	Minimal
Technical characteristics		
Flow driver	Integrated (on-board air compressor)	
Oxygen flow capacity	0–10 LPM	
Pressure	5–8 cm H_2O	
Total blended flow	0–10 LPM	
Humidification	Heated humidification	None
Alarms	Audio and visual	Audio power
Purchasing		
Accessories	Non-proprietary	Proprietary
Consumables	Reusable	Available
Instrument pricing (without shipping costs)	<US$1,000	<US$2,000
Utility requirements		
Power source	Mains with battery backup	Mains
Battery	Rechargeable	None
Voltage	Matches that available in purchasing country	

that the introduction of CPAP improved neonatal survival (81). Pooled data from four of the observational studies showed 66% reduction in in-hospital mortality among preterm neonates following introduction of CPAP (odds ratio 0.34, 95% confidence interval 0.14–0.82) (81).

In 2020, UNICEF published a target product profile to align CPAP innovators and other stakeholders to the most important performance and operational characteristics, as well as target pricing to aid in the development of effective and safe CPAP devices that can be scaled (88). Excerpts from this profile are shown in Table 1. Some technical characteristics for optimal CPAP devices include the ability to produce CPAP pressure between 5 and 8 cm H_2O, provide humidification, blend oxygen, and have flow capacity of 0–10 L/min. Table 2 compares the characteristics of different categories of CPAP devices available in LMIC to the highest cost devices which fulfill the requirement of UNICEF's CPAP target product profile (89).

The only published LMIC randomized trial of CPAP among neonates was conducted in Tanzania, in which 48 preterm infants with birth weight >1,000 g with RDS were randomized to receive CPAP *via* the Pumani device (25 subjects) or oxygen (23 subjects). The study found that survival to hospital discharge in the CPAP and oxygen groups respectively was not statistically significant [68 vs. 47.8%, crude OR 2.3 (95% CI 0.72–7.49)]. However, in the per-protocol analysis a more significant number of subjects in the CPAP group survived to hospital discharge 77.2 vs. 47.8% (crude OR 3.7, 95% CI 1.02–13.47). The study reported no pneumothoraxes, but that bleeding from the nose was more common in the CPAP group (94).

Other available evidence on the benefits of CPAP from LRS include three trials conducted in children who were between 1 month to 5 years of age with diagnoses other than RDS. The first trial conducted in Ghana was a cross over trial between two secondary hospitals and included over 2,000 subjects with clinical signs of respiratory distress. The primary outcome measure was all-cause mortality at 2 weeks after enrollment. The study found that 3% (26/1,021) patients in the CPAP group, and 4% (44/1,160) patients in the control group died [relative risk (RR) of mortality 0.67, 95% CI 0.42–1.08; $p = 0.11$] (95). The second was conducted in Bangladesh and randomized children with a diagnosis of severe pneumonia and hypoxemia to receive oxygen therapy by either bubble CPAP, standard low-flow nasal cannula (2 L/min), or high-flow nasal cannula (2 L/kg per min up to the maximum of 12 L/min). Significantly fewer children in the bubble CPAP group had treatment failure than in the low-flow oxygen therapy group (relative risk 0.27, 99.7% CI 0.07–0.99; $p = 0.0026$) (96). The third trial was conducted in Malawi, and 323 children were randomly assigned to oxygen and 321 to bCPAP. The results showed that CPAP was associated with increased risk of mortality compared with oxygen therapy, 53 (17%) of 321 vs. 35 (11%) of 323 (relative risk 1.52; 95% CI 1.02–2.27; $p = 0.036$) (97).

The lack of standard equipment and high-quality trials have limited access to CPAP among preterm neonates with RDS in LRS. There are also practical barriers to the widespread use of CPAP in LMICs. In a systematic study on facilitators and barriers to implementation of CPAP in LMICs, the authors reported staff shortage and high staff turnover limited the uptake and use of CPAP (76). The study also reported that parents were resistant to the use of CPAP because of local beliefs that oxygen use led to poor outcomes (76).

Oxygen blending

Supplemental oxygen is a key RDS treatment modality whether used through nasal cannula, CPAP or mechanical ventilation (98). However, oxygen use among neonates in particular can have deleterious effects and current evidence is that titration of fraction of inspired oxygen to achieve saturations as measured by pulse oximetry between 90 and 95% provides the optimal balance between the therapeutic benefits of oxygen and the risk of oxygen toxicity (45). When used in excess, oxygen can cause oxidative injury to a premature baby's lungs, eyes and brain (99). Use of 100% oxygen with premature infants is a major risk factor for the development of retinopathy of prematurity (ROP) which can lead to visual impairment and even blindness among survivors (45). This is especially important in CPAP and mechanical ventilation where all of the baby's inspired gas is from the respiratory circuit and there is no entrainment of room air around a nasal interface or mask. Most

TABLE 2 Comparison of features and cost of CPAP device categories in use in LMIC.

	Improvised circuits	Low-cost	Medium cost	High cost
Required flow source	Oxygen			Pressurized oxygen and air
Oxygen blending	No	Yes		
Humidification	Passive (bubble bottle) and entrained ambient humidification			Heated humidified air
Patient interface	Nasal cannula	Hudson prong or RAM cannula	Proprietary prongs, RAM cannula or Hudson prong	Proprietary prongs/mask, RAM cannula or Hudson prong
Tubing and interface resistance	High (tubing and nasal prongs)	May include high resistance components	Low	Low
Electricity requirement	None for device. Is needed for oxygen concentrator if used and pulse oximeter.		Required	
Consumables	Single use cannula	Single and multi-use components	Single and multi-use components	Single use components
Cost (USD)	$1–4	$20– $800	$1,000–2,000	$3,000–6,000+
Example devices	WHO (83)	Vayu (90) PATH (77)	Pumani (91) Diamedica (92) Polite (93)	Fisher-Paykel (89) Dolphin (70) Phoenix (71)

Updated from reference (72).

low resource facilities treating newborns with CPAP use 100% oxygen because they do not have a source of compressed air to blend with oxygen (73, 74, 100). The well-intentioned use of oxygen therapy to save preterm newborn lives in LRS could lead to an epidemic of ROP-related blindness in sub-Saharan Africa, as already suggested in Latin America, South Africa, India and China (101–104). Methods to ensure safe use of oxygen, with blending of air to optimize the fraction of inspired oxygen are urgently needed (66). Recent WHO guidelines for the care of small and sick newborns recommend retinal exams for preterm infants to detect ROP and efforts to scale up this screening are underway (45, 105). Unfortunately, ophthalmologists trained in these exams are sparsely distributed (106).

Several options exist for the provision of blended oxygen to newborns with varying cost and availability (Table 3). High resource settings and some tertiary facilities in LRS use precision oxygen blenders; however, these are expensive and require high pressure sources of air and oxygen flow. Some medium cost commercialized CPAP devices designed for lower resource settings include on-board air compressors. When used in combination with an oxygen source, these devices can provide flow with oxygen concentrations ranging from 21 to 100% when available (92–94).

To address the remaining gap in safe oxygen therapy, low-cost modalities to blend oxygen and air are in development. One type of device entrains room air into a flow of oxygen *via* the Bernoulli principle and therefore does not require compressed air (77, 107, 108). Initial studies of these devices are in progress and show promise in their efficacy, portability, cost, and usability. This entrained air mechanism, however, is limited to providing fraction of inspired oxygen in pressurized flow of less than ∼30% because of the pressure drop associated with increasing entrainment of room air (107).

An important consideration for provision of blended oxygen is the increased importance it places on pulse oximetry and measurement of patient saturations to guide blending at the bedside. Pulse oximetry is included as a recommendation in the WHO standards for care of the small newborns and is best used continuously to allow frequent detection of low or high saturations and resultant adjustment in oxygen concentration (45). However, oximetry devices are expensive and remain a limitation for safe provision of CPAP and oxygen (74, 111).

Methylxanthines

In addition to RDS, apnea of prematurity (AOP) commonly affects premature infants. It is defined as cessation of breathing with hypoxia and bradycardia that last more than 15 s (112). The severity and frequency of AOP are inversely related to the degree of prematurity (112, 113). Methylxanthines—aminophylline, theophylline, and caffeine citrate (caffeine)—are the mainstay pharmacologic treatments for AOP used adjunctively with positive pressure ventilation (114). The pharmacological effects of methylxanthine include (i) stimulation of the respiratory

TABLE 3 Oxygen blending modalities for CPAP in low resource settings.

	No blending	Blending *via* ambient air entrainment device	Blending *via* air compressor in CPAP device	Blending with high pressure (wall) sources
Range of percent oxygen	100%	30–100%	21–100%	21–100%
Availability in low resource facilities	Most frequently used	Not yet commercially available	Increasingly in use	Generally limited to tertiary facilities
Components Required	–	–	Medium cost CPAP device or stand-alone air compressor	High precision blender
	Oxygen tank or concentrator	Oxygen tank or concentrator	Oxygen tank or concentrator	**High pressure** air and oxygen sources
Relative Cost	$	$$	$$$	$$$$$
Example devices	WHO (83)	PATH (77) Vayu (107) Minnesota (108)	Pumani (94) Diamedica (92) Polite (93)	Precision medical (109) Bio-med devices (110)

center in the medulla; (ii) increased sensitivity to carbon dioxide; (iii) increased skeletal muscle tone; (iv) enhanced diaphragmatic contractility; (v) increased minute ventilation; (vi) increased metabolic rate; and (vii) increased oxygen consumption (115–117). Caffeine and aminophylline are equivalent in reducing events of AOP (118). However, caffeine has a wider therapeutic index, longer half-life that allows once-daily administration, does not require drug-level monitoring, and has a better side effect profile—causing less tachycardia and feeding intolerance (118, 119). Furthermore, compared to placebo, caffeine shortens ventilator days, reduces the risk of developing bronchopulmonary dysplasia, improves neurodevelopment at 18–24 months, and is cost-effective (120–123). Furthermore, theophylline therapy has been associated with seizures and hypokalemia in neonates (124).

Caffeine for AOP treatment first appeared in the 2009 WHO essential drug list (125). Despite this, the use of caffeine to treat preterm babies in low resource settings has not achieved scale (126). In a survey of 55 clinicians from 13 countries in sub-Saharan Africa, only six countries used caffeine, and often inconsistently (126). In a review of 11 studies on caffeine for premature infants, the only studies from LMICs were from India (127). The reasons for the unavailability of caffeine in SSA are complex, including high drug prices, stock outs, and the drugs is not obtainable for purchase in some countries (126). Additionally, there may be less demand for caffeine as knowledge of greater safety over aminophylline may not be pervasive. Furthermore, the patient population where the benefits of methylxanthines are greatest (very-to-extreme preterm infants), have very poor survival in LMICs. The availability of overall care for these patients varies greatly between these low resource sites and that in HIC where the caffeine trials were conducted (120, 128).

Surfactant

Exogenous surfactant replacement therapy is the definitive pharmacologic treatment for RDS (129). Used adjunctively with invasive or non-invasive ventilation, the use of surfactant reduces RDS specific neonatal mortality (130). WHO recommends that small and sick neonates be assessed for surfactant deficiency, and treatment provided within 2 h of birth (45). Exogenous surfactant preparations include synthetic surfactants and natural surfactants derived from animal sources. Early trials suggested that natural surfactants are more efficacious than synthetic preparations, with the benefit attributed to the proteins in natural preparations (131). However, synthetic surfactants can be produced at lower cost, and newer synthetic surfactants are being developed and evaluated, showing promise for their equivalency to natural surfactants (132, 133).

Surfactant use is limited in low resource settings; particularly, sub-Saharan Africa (74, 134). In a systematic review on the use of surfactant in LMICs, of 38 relevant studies, none were from Sub-Saharan Africa (SSA) (135). In a survey involving respondents from 49 African countries, surfactant was available in 33% and 39% of the most well-equipped public and private hospitals, respectively (74). Potential explanations for the limited use of surfactant in LMICs includes unavailability, cost, and the perception that surfactant therapy must occur in conjunction with mechanical ventilation (MV) which may not be available or feasible (74). In the survey of African respondents, the cost of a vial of surfactant varied from <US$200 to over US$500.

Traditional surfactant replacement therapy involves instillation *via* endotracheal tube, which requires significant skill on the part of the provider, and adjunctive use of MV. However, given the association of MV with adverse outcomes (136–138), in current neonatal practice, clinicians strive to limit

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or avoid mechanical ventilator use. This change in practice has led to innovative ways to administer exogenous surfactant in minimally invasive ways. Examples of these techniques include dosing surfactant *via* a thin catheter, a laryngeal mask airway (LMA), or using nebulized or aerosolized surfactant. LMAs, of note, are generally designed for use among neonates >2,000 g, and studies on surfactant instilled *via* LMA have not included preterm newborns <1,250 g (139).

Evidence from high-income settings indicates that instillation of surfactant through a thin catheter (140, 141) or LMA method (142, 143) can prevent the need for intubation when compared to treatment with continuous positive airway pressure alone. When pooled in a meta-analysis, these minimally invasive techniques (administration *via* LMA or thin catheter) are associated with a 47% risk reduction in CPAP failure, when compared with CPAP alone (141–144) (Figure 3). Surfactant instillation *via* thin catheter is included in the 2019 European consensus guidelines on the management of respiratory distress syndrome (145, 146). Data from the German Neonatal Network indicated that over 50% of surfactant replacement therapy occurs with the thin catheter method (147). Results on the efficacy and feasibility of nebulized surfactant is emerging (148). In a recent randomized controlled trial, nebulized surfactant did not differ from CPAP alone in preventing CPAP failure, however with advances in nebulization/aerosolization devices and surfactant formulations, this modality may have promise (149).

Data from a survey conducted among 49 African countries on the availability of neonatal respiratory care showed that 11% (4/35) of NICUs capable of providing surfactant replacement therapy did so with the thin catheter method (74). There are no randomized trials originating from a LMIC on the use of minimally invasive surfactant administration. The only available study from Sub Saharan Africa is an observational study from Asaba, Nigeria that compared mortality among preterm infants with respiratory distress treated with CPAP who were administered surfactant *via* thin catheter compared with those who did not receive surfactant. Eligibility included parent's ability to pay for the surfactant, resulting in only 25% ($n = 51$) of neonates to be able to receive the medication. The study reported a significant reduction in mortality with surfactant administration only among neonates with birth weight below 28 weeks and 1 kg birthweight [50% (13/26) vs. 65% (35/54)] (151). Further studies on less invasive strategies for administration of exogenous surfactant in LRS are urgently needed.

Mechanical ventilation

Oxygen therapy with CPAP for RDS is the most prevalent form of respiratory support in LMIC (74, 100). However, in a systematic review that included eight observational studies from LMIC on the use of CPAP and enrolling patients of varied degrees of prematurity, 20–40% of infants with RDS failed CPAP treatment in the absence of surfactant therapy (81). These patients failing CPAP require surfactant administration and mechanical ventilation (MV) for improved survival. In a survey on available respiratory support modalities for RDS from Africa, of the 49 countries with at least one respondent, only 49% of the most well-equipped government hospitals and 59% of the most well-equipped private hospitals located in capital cities used MV (74). A survey from Nigeria suggests sparse availability and lack of capacity to use MV devices where available (152, 153). We speculate that the findings of this survey can be generalized to other LMICs. Most global recommendations and predictive models of interventions to improve prematurity related mortality in LMICs do not include MV, only CPAP and there is a need to elucidate the residual mortality from RDS which could be averted with MV (45, 154).

The cost of MV and lack of capacity to use MV are deterrents to its use (74). MV is not a standalone intervention; medications like surfactant, caffeine, and antenatal steroids improve outcomes of neonates managed on MV. Furthermore, the use of blended oxygen, oximetry, arterial blood gas, mobile chest x-rays, respiratory therapists, neonatal nurses, biomedical technicians, and pharmacologic support are critical for safe and effective use of MV but are limited in LMIC. MV is currently not taught and not incorporated into undergraduate training of medical and nursing schools in several LMICs (74, 155). Furthermore, postgraduate clinical exposure and training on MV is limited; hence knowledge of MV among the essential workforce is deficient. Data on MV's safety and efficacy in LMIC is currently lacking; this area needs further exploration.

During the COVID-19 pandemic, the lack of, and need for MV generated awareness of its necessity in LMICs among patient populations outside of the neonatal period (156–158). The pandemic also sparked the production of more basic, compact, and affordable MV devices by academic institutions and industry (159–161). The increased access to, and availability of MV in some centers may increase its use in newborn respiratory support which should be done with caution.

Fluid and nutrition

Adequate nutrition is critical for the continued growth and development of the premature respiratory system. Premature infants are at risk of insensitive water losses and nutritional failure by virtue of their dermal and intestinal immaturity. Liberal or excessive fluid administration is associated with poor respiratory outcomes in preterm infants (162), and optimal early nutrition is correlated with a better pulmonary outcome (163). Hence careful consideration of fluid management, and optimizing nutrition in premature infants is essential to RDS management.

[Method] Study	Intervention group n/N[1]	Control group n/N	Weight (%)[3]	Odds Ratio M-H, Random, 95% CI[2]
[LMA] Roberts et al, 2018	19/50	34/53	21%	0.34 (0.16 – 0.77)
[LMA] Attridge et al, 2013	1/13	3/13	4%	0.36 (0.05 – 2.88)
Subtotal (95% CI)				*0.35 (0.17 – 0.74)[5]*
[Thin Catheter] Dargaville et al, 2021	88/241	176/244	32%	0.22 (0.15 – 0.33)
[Thin Catheter] Gopel et al, 2011	30/108	51/113	44%	0.47 (0.24 – 0.82)
Subtotal (95% CI)				*0.32 (0.15 – 0.65)[5]*
[Combined] Total	**138/412**	**264/423**	**100%**	**0.32 (0.21 – 0.49)[4]**

Test of heterogenicity Chi square= 4.94, df=3 (p=0.18)

[1]N= total number in group, n= number in group with outcome (CPAP failure)
[2]Outcome of interest in picture and number. Random effect model used for meta-analysis
[3]Influence of studies on overall meta-analysis.
[4]Overall effect.
[5]Subgroup pooled effect.

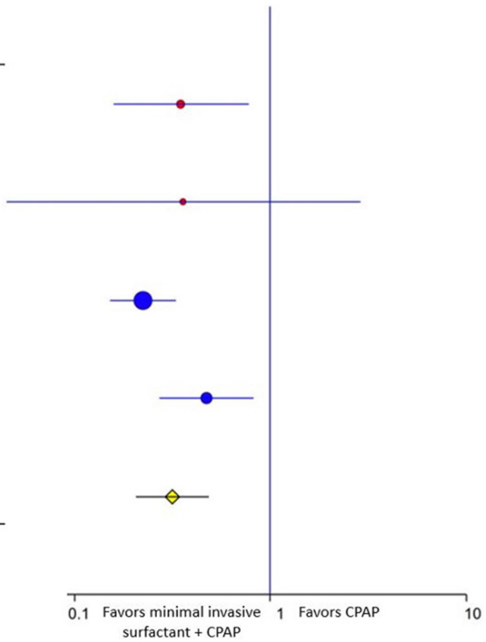

FIGURE 3
Forest plot of comparison of CPAP plus minimally invasive surfactant administration *via* thin catheter or laryngeal mask airway (LMA) vs. CPAP only. The outcome of interest was CPAP failure as determined by need for intubation. These minimally invasive techniques are associated with a 47% risk reduction in CPAP failure (142–144, 150).

Discussion

To achieve the sustainable developmental goals targets, small and sick newborns need high-quality inpatient care at the right time and in the right place (8). Transformative RDS therapies, which are standard of care in high resource settings (HRS), significantly reduce prematurity-related mortality. However, 40–60 years after these interventions were proven effective, about 2.4 million small and sick newborns born in LMICs will die this year because of lack of access. The resource limitations in LMICs that affect medication and equipment availability and the ancillary care required to reap their benefits are poor or non-existent. Consequently, our knowledge on the impact of these RDS-specific interventions in LRS is limited. Important questions that remain include:

1. how women at risk of preterm labor in rural communities can be treated safely with ACS and have the desired pregnancy outcome?
2. how can low-cost CPAP devices be optimized to be as effective and safe as the gold standard devices?
3. how can providers learn and maintain direct laryngoscopy skills and the complexities of MV?
4. how can the cost of essential medications like surfactant, caffeine, and devices like CPAP and MV be made more affordable, so they are accessible to providers in LMICs?

To bridge this knowledge gap, thoughtful research designs are required. Research needs to focus equally on implementation as well as evidence generation, taking into context the resource limitations of the clinical setting (164). These type of research studies will allow accurate determination of the extent to which timely and effective neonatal transport, thermoregulation, nutritional support, hypoglycemia management, infection control, and provider-to-patient ratios affect the benefits of these evidence-based RDS-specific therapies. Also, the use of telemedicine proved beneficial during the COVID-19 pandemic where face to face physician patient interaction was limited. Indeed, telemedicine has been used to provide simulation training effectively and feasibly for neonatal resuscitation skills (165, 166). Opportunities to leverage telemedicine in overcoming some of the highlighted barriers is an area for further exploration.

Most global recommendations and predictive models of interventions to improve prematurity-related mortality in LMICs indicate that the greatest benefit will only be achieved with a comprehensive approach to implementing these evidence-based interventions (45, 154). Critical to the impact of any RDS-specific interventions are the core elements of neonatal care including thermoregulation, KMC, safe and adequate transportation to facilities capable of providing high-quality care, infection management, fluid and nutritional support, and workforce availability and capacity. Meeting the ENAP coverage target for care of small and sick newborns in facilities that can provide basic RDS-specific management like optimal resuscitation and CPAP in 80% districts will require considerable investment. The target will be more attainable with further development of low cost, safe and reliable RDS-specific drugs and devices; broader availability consumable parts, standardization of training, guidelines for optimal and safe use, in addition to adequate staffing to provide this level of care (7, 75, 167). To accelerate the development of solutions essential to make the global coverage target feasible, governments may consider providing incentives for local and international biomedical companies to enable them to safely and effectively produce and market their products locally. These incentives could include tax exemptions, streamlined in-country product registration and evaluation by regulatory bodies.

Conclusion

Respiratory distress syndrome is a major driver of prematurity related neonatal mortality. High quality trials conducted in HRS have shown interventions to be effective in reducing the RDS specific neonatal mortality. However, these standard of care interventions in HRS have sparse and sporadic coverage in LRS. When tested in LRS these interventions have not consistently had the same beneficial effect, likely due to the lack of critical ancillary services and core neonatal care practices. To achieve a neonatal mortality rate as low as 12 per 1,000 live births in year 2030 (8), guided by high quality implementation and effectiveness research, considerable scale up of RDS-specific interventions bundled with core neonatal care practices are needed.

Author contributions

OE, MB, and AH conceptualized the review. Initial draft by OE, IO, and AH with revisions by MB. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a shared committee with one of the authors MB.

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EDITED BY
Susan Coffin,
University of Pennsylvania,
United States

REVIEWED BY
Kosmas Sarafidis,
Aristotle University of Thessaloniki,
Greece
Peter Cooper,
University of the Witwatersrand,
South Africa

*CORRESPONDENCE
Marcia Mangiza
mmangiza@yahoo.com

†PRESENT ADDRESS
Marcia Mangiza,
Department of Paediatrics,
Sally Mugabe Central Hospital, Harare,
Zimbabwe

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Morbidity and mortality in small for gestational age very preterm infants in a middle-income country

Marcia Mangiza[1*†], Danielle E. Y. Ehret[2,3], Erika M. Edwards[2,3,4], Natasha Rhoda[1] and Lloyd Tooke[1]

[1]Groote Schuur Hospital, Department of Paediatrics, University of Cape Town, Cape Town, South Africa, [2]Vermont Oxford Network, Burlington, VT, United States, [3]Department of Paediatrics, Larner College of Medicine, University of Vermont, Burlington, VT, United States, [4]Department of Mathematics and Statistics, University of Vermont, Burlington, VT, United States

Objective: To evaluate the impact of small for gestational age (SGA) on outcomes of very preterm infants at Groote Schuur Hospital (GSH), Cape Town, South Africa.

Study design: Data were obtained from the Vermont Oxford Network (VON) GSH database from 2012 to 2018. The study is a secondary analysis of prospectively collected observational data. Fenton growth charts were used to define SGA as birth weight < 10th centile for gestational age.

Results: Mortality [28.9% vs. 18.5%, adjusted risk ratio (aRR) 2.1, 95% confidence interval (CI) 1.6–2.7], bronchopulmonary dysplasia (BPD; 14% vs. 4.5%, aRR 3.7, 95% CI 2.3–6.1), and late-onset sepsis (LOS; 16.7% vs. 9.6%, aRR 2.3, 95% CI 1.6–3.3) were higher in the SGA than in the non-SGA group.

Conclusion: Small for gestational age infants have a higher risk of mortality and morbidity among very preterm infants at GSH. This may be useful for counseling and perinatal management.

KEYWORDS

small for gestational age, low- and middle-income countries, very low birth weight (VLBW), bronchopulmonary dysplasia, late onset sepsis, preterm

Introduction

Small for gestational age (SGA) is defined as a birth weight that is below the 10th percentile for gestational age (1). SGA includes infants who are constitutionally small and those who have intrauterine growth restrictions due to environmental or genetic factors (2).

Small for gestational age is commonly used as a proxy for intrauterine growth restriction and, in settings with a high prevalence of SGA, it is more likely to be a result of intrauterine growth restriction rather than being constitutionally small (3). Intrauterine growth restriction is more prevalent in low- and middle-income countries (LMICs) (4), due to contributing factors, such as poor maternal nutrition, young maternal age, maternal infections, and short birth spacing (5–8). Approximately one in five infants born in LMICs is SGA (4). Despite this high prevalence of SGA, the outcomes of preterm babies have not been well described in these settings.

In LMICs, mortality risk associated with being premature and SGA is substantially higher than for either alone, with these infants having a 10–40 times higher risk of mortality in the first month of life when compared with term and appropriate for gestational age infants (9). We sought to evaluate the impact of SGA on the outcomes of very low birth weight (VLBW) and very preterm (<32 weeks) infants at the Groote Schuur Hospital (GSH) neonatal unit in Cape Town, South Africa. Our objectives were to compare rates of in-hospital mortality and neonatal morbidities of SGA preterm infants with non-SGA preterm infants and to compare outcomes of symmetrical vs. asymmetrical infants with SGA.

Materials and methods

The study is a secondary analysis of prospectively collected observational data. GSH is a public hospital with a highly specialized public neonatal unit. There are 75 neonatal beds of which 20 are for intensive care. The neonatal unit admits up to 2,000 babies a year and approximately 500 infants are VLBW. We obtained data from the Vermont Oxford Network (VON) GSH database from 2012 (when we joined the Network) to 2018. VON is a non-profit, voluntary worldwide collaboration dedicated to improving the quality, safety, and value of neonatal intensive care (10). The database includes items, such as respiratory support in the delivery room, in the neonatal intensive care unit, and at discharge; other procedures and interventions, such as surgery; morbidities and mortality; length of stay; infant and maternal characteristics; and status at discharge. The GSH VON VLBW database enrolls neonates with birth weights between 401 and 1,500 g if they are born at GSH or transferred there within the first 28 days of life. Infants that are subsequently transferred from GSH to other hospitals are followed up to document mortality and mortality prior to discharge in the GSH VON VLBW database. Our study included infants born from 27 weeks 0 days to 30 weeks 6 days gestational age in order to capture both SGA and appropriate for gestational age (AGA) for the weight category 501–1,500 g. We excluded neonates with major congenital or chromosomal anomalies. The study was approved by the Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town (R117/2020).

Study variables

Small for gestational age was defined as a birth weight below the 10th centile and non-SGA as birth weight ≥the 10th centile using sex-specific Fenton growth charts (11). Non-SGA comprised of AGA was defined as between the 10th and 90th centile and large for gestational age (LGA) was defined as >90th centile on the sex-specific Fenton growth charts. Gestational age was estimated using early ultrasound (<20 weeks) as the gold standard. Ballard score or postnatal foot length (12) were used when early ultrasound was not available. Symmetric SGA was defined as both birth weight and head circumference below the 10th centile on the Fenton growth chart and asymmetric SGA when birth weight was below the 10th centile and head circumference was above the 10th centile for gestational age on the Fenton growth chart.

Infants were considered to have exposure to antenatal corticosteroids if betamethasone, dexamethasone, or hydrocortisone was administered intramuscularly or intravenously to the mother during pregnancy at any time prior to delivery. Mothers were reported to have received prenatal care if any obstetric care was provided prior to the admission during which the birth occurred. Maternal hypertension was defined as chronic or pregnancy-induced hypertension (above 140 systolic or 90 diastolic), with or without edema or proteinuria. Eclampsia and pre-eclampsia were considered the forms of pregnancy-induced hypertension.

Mortality was defined as death before discharge home. Respiratory distress syndrome (RDS) was defined as respiratory distress from birth with the need for >35% Fio_2 in the first 48 h of life despite continuous positive airway pressure (CPAP) or invasive mechanical ventilation. Papile's criterion (13) was used to define intraventricular hemorrhage (IVH) noted on cranial ultrasound scan and severe IVH was defined as grades 3 and 4. Bronchopulmonary dysplasia (BPD) was defined as the requirement of oxygen and/or respiratory support at 36 weeks post-menstrual age or, if discharged at 34 or 35 weeks, oxygen requirement at discharge (14). Severe retinopathy of prematurity (ROP) was defined as grades 3–5 (15) documented by an ophthalmologist's examination, with the worst stage examination in the eye with the most advanced stage recorded. Early onset sepsis was defined as recovery of a bacterial organism on a specified list from blood or cerebrospinal fluid culture within 3 days of birth. Late-onset sepsis (LOS) was defined as recovery of a bacterial organism on a specified list from blood or cerebrospinal fluid culture, coagulase negative staphylococcal infection, or fungal organism after day 3 from birth; coagulase negative staphylococcus also required signs and symptoms of infection and at least 5 days of antibiotic therapy (16). Necrotizing enterocolitis (NEC) was diagnosed by the clinical team at surgery, post-mortem, or clinically and radiographically using standard criteria from the VON Manual of Operations Definitions (16).

TABLE 1 Demographic features of the study population of infants who were born 27–30 weeks + 6 days gestational age and 501–1,500 g from 2012 to 2018.

	SGA (N = 239)	Non-SGA (N = 1640)
Gestational age (weeks), mean (SD)	29 (1)	29 (1)
Birth weight (grams), mean (SD)	799 (119)	1083 (182)
Head circumference at birth (cm), mean (standard deviation)	24 (2)	26 (2)
Maternal hypertension (%)	60.1	40.4
Antenatal steroids (%)	73.6	66.4
Female (%)	52.7	48.4
Prenatal care (%)	87.5	82.4
Inborn (%)	91.2	85.4

SD, standard deviation.

Analyses

All analyses were conducted in Statistical Analysis System 9.4. Logistic regression with a Poisson distribution and log link was used to produce risk ratios for each outcome adjusted for sex, antenatal steroid exposure, inborn/outborn status, and gestational age in weeks (17). All adjustors, identified *a priori*, were included in each model without stepwise or backward selection.

Results

Characteristics of the study population

A total of 1,879 infants with VLBW between the gestational ages of 27 weeks 0 days and 30 weeks 6 days were admitted to GSH NICU between 2012 and 2018. The prevalence of SGA among the study population was 12.7%. The mean gestational age for both infants with SGA and non-SGA was 29 weeks. The mean birth weight in the SGA group was 799 and 1,083 g in the non-SGA group. The majority (99%) of the non-SGA group was AGA with only 20 infants being LGA. The mothers of infants with SGA were more likely to have received antenatal steroids (73.6% vs. 66.4%) and to have hypertension (60.1% vs. 40.4%). **Table 1** depicts the demographic features of the study population based on SGA status. **Figure 1** shows the proportion of infants with SGA at each gestational age.

Neonatal morbidity and mortality

During the study period, 372 of the infants demised before being discharge home with an overall mortality rate of 19.7%. The mortality rate was significantly higher in the SGA group at 28.9% vs. 18.5% [adjusted risk ratio (aRR) 2.1, 95% confidence interval (CI) 1.6–2.7] when compared to the non-SGA group. BPD, NEC, and LOS were significantly higher in the SGA group. **Table 2** shows the incidence of neonatal morbidity and mortality in SGA vs. non-SGA VLBW neonates.

Table 3 shows the incidence of neonatal morbidities among survivors in the study population. Among survivors, only BPD and LOS remained statistically significant, with both morbidities occurring more frequently in the SGA group. The total length of stay among survivors was a median of 42 days [interquartile range (IQR) 28, 56] for infants with SGA and a median of 41 days (IQR 25, 56) for infants with non-SGA.

Among the infants with SGA, 217 were categorized into symmetrical (97; 45%) and asymmetrical (120; 55%) SGA (22 infants were missing birth head circumference). There were no statistically significant differences in mortality or morbidities when these two groups were compared.

Discussion

In our study population, 12.7% of the infants were SGA as defined as weight less than the 10th centile at birth by the Fenton growth charts (11). This is higher than the prevalence in two studies done in high-income countries, which found an SGA prevalence of 9% among infants 501–1,500 g (18) and 10% among infants 22–29 weeks (19). Our finding is in support of studies that have documented SGA to be more prevalent in resource-limited countries (4).

We found the mortality rate to be significantly higher among infants with SGA as compared to infants with non-SGA. The increased risk of mortality is similar to the mortality that Li-Yi Tsai et al. found in Taiwan, which was a middle-income country at that time (20). Overall mortality rate in the Taiwanese study was less than our study (14.7% vs. 19.7%), although the Taiwanese study did include infants till 32 weeks gestation. Several studies in high-income countries have evaluated the association of SGA status with the outcomes of infants with VLBW. These analyses have differing conclusions depending on the basis of the comparison groups, by gestational age at birth or by birth weight. In a study including VON member hospitals in the United States of America (United States), Boghossian et al. found an increased risk of mortality among infants with SGA born at 22–29 weeks' gestational age and they noted that mortality was, however, not homogenous across gestational ages (19). In contrast to our findings, Horbar et al. found that SGA status was associated with an increased likelihood of survival among infants with VLBW in the first 28 days at participating VON member hospitals in the United States (21). The analyses in this study, however, were based on birth weight rather than gestational age. The authors concluded that SGA had a lower risk of mortality

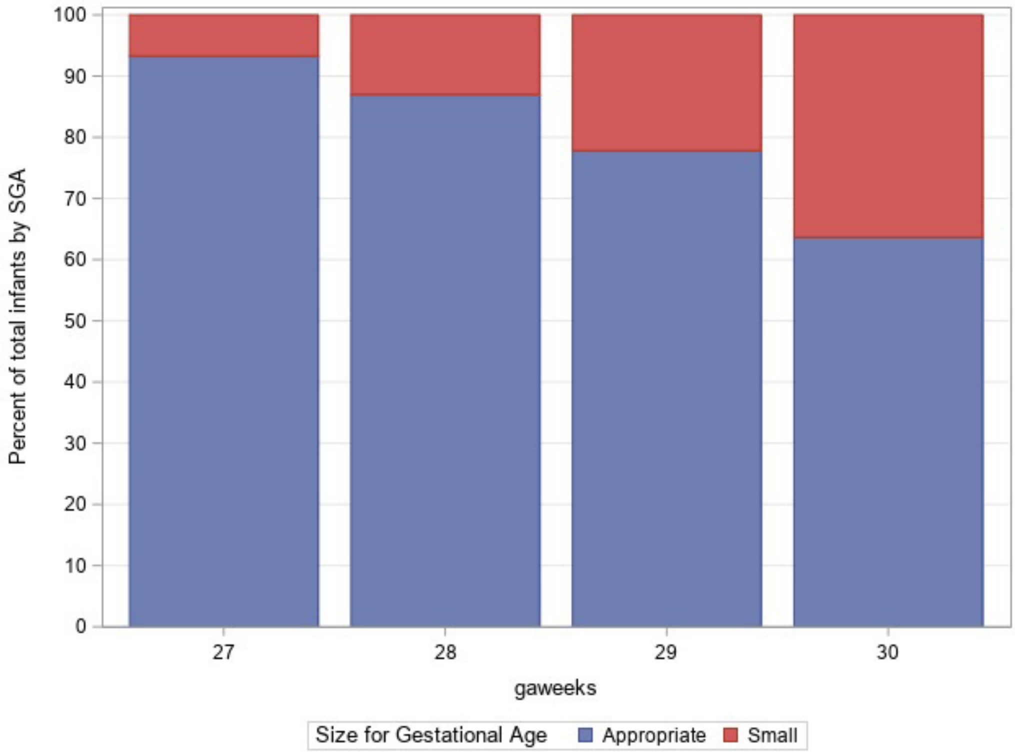

FIGURE 1
Percent of total infants by small for gestational age (SGA; red) and non SGA (blue).

TABLE 2 Incidence of neonatal morbidity and mortality in very low birth weight infants classified as small for gestational age (SGA) or appropriate for gestational age (AGA). Risk ratios for the association between SGA and non-SGA (reference group) adjusted for sex, antenatal steroids, and gestational age at birth.

	SGA (N = 239)	Non-SGA (N = 1640)	aRR (95% CI)
	n/N (%)	n/N (%)	
MORTALITY	69/239 (28.9)	303/1640 (18.5)	2.1 (1.6, 2.7)
RDS	103/238 (43.3)	764/1632 (46.8)	1.0 (0.8, 1.3)
BPD	24/171 (14.0)	61/1343 (4.5)	3.7 (2.3, 6.1)
IVH (Grades III, IV)	10/211 (4.7)	116/1512 (7.7)	0.8 (0.4, 1.6)
NEC	24/238 (10.1)	107/1632 (6.6)	1.7 (1.1, 2.7)
ROP (Stages III–V)	4/78 (5.1)	15/579 (2.6)	3.2 (1.0, 10.2)
Early onset sepsis	2/238 (0.8)	30/1632 (1.8)	0.5 (0.1, 2.1)
Late onset sepsis	36/216 (16.7)	146/1522 (9.6)	2.3 (1.6, 3.3)

RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

than AGA at any given birth weight, recognizing that these infants were more mature, with older gestational ages at birth. This distinction in analyses is important as gestational dating of pregnancies in LMIC is improving (22), allowing for better characterization of preterm risks. Our study, therefore, compared infants based on gestational age using a hierarchy of early ultrasound, followed by postnatal examination with Ballard score or foot length. In infants with extremely low birth weight (ELBW) in United Kingdom, Charles et al. found no difference in mortality between SGA and AGA even after correcting for gestational age (23). Their study population was more premature than ours with generally higher mortality. Although the ELBW population is a high-risk group globally, they do not represent the focus of neonatal improvement efforts in LMICs, hence the VLBW inclusion in our study.

TABLE 3 Incidence of neonatal morbidities among survivors in very low birth weight infants classified as small for gestational age (SGA) or non-SGA. Risk ratios for the association between SGA and appropriate for gestational age (AGA; reference group) adjusted for sex, antenatal steroids, and gestational age at birth.

	SGA (*N* = 170)	Non-SGA (*N* = 1337)	aRR (95% CI)
	n/*N* (%)	*n*/*N* (%)	
RDS	53/170 (31.2)	538/1336 (40.3)	0.9 (0.7, 1.2)
BPD	24/170 (14.1)	56/1328 (4.2)	4.0 (2.5, 6.7)
IVH (Grades III, IV)	1/168 (0.6)	45/1280 (3.5)	0.2 (0.0, 1.6)
NEC	10/170 (5.9)	54/1336 (4.0)	1.7 (0.9, 3.5)
ROP (Stages III–V)	3/77 (3.9)	15/568 (2.6)	2.5 (0.7, 9.2)
Early onset sepsis	2/170 (1.2)	16/1336 (1.2)	1.1 (0.2, 5.0)
Late onset sepsis	26/170 (15.3)	86/1331 (6.5)	3.3 (2.1, 5.2)

Levels of BPD are very low at GSH (24) but we found an increased risk of BPD among infants with SGA, 14% vs. 4.5% in the non-SGA group. This finding is in keeping with other studies, which have found the risks of BPD to be 2- to 6-fold higher among infants with SGA (23, 25, 26). Proposed mechanisms for the increased risk of BPD include exposure to pro-inflammatory cytokines both prenatally and immediately postnatally in addition to malnutrition (27). Despite having an increased risk of BPD, there was no statistically significant difference in RDS between the infants with SGA and non-SGA. It is postulated that in infants with SGA, the incidence of RDS is much lower because of increased corticosteroid production as a result of exposure to prenatal stress (28). Despite a higher percentage of antenatal steroids in the SGA group as compared to the AGA group, the incidence of RDS was not lower in the infants with SGA. Our clinical definition of RDS could have captured additional respiratory pathology unrelated to surfactant deficiency, such as congenital pneumonia and respiratory distress due to sepsis, and therefore masked a true difference in RDS. However, in a study including US member hospitals of VON, Boghossian et al. found no difference in the incidence of RDS between infants with SGA and non-SGA who had not received antenatal steroids and for those who received antenatal steroids, the incidence of RDS was higher among the SGA group (19).

Necrotizing enterocolitis is the most serious gastrointestinal complication affecting infants with VLBW. The risk of NEC was higher in the SGA group when looking at the entire study population but when we analyzed the risk among survivors the difference between the groups did not reach statistical significance. This finding suggests a high mortality for SGA babies who develop NEC. Bhoghossian et al. also found an increased risk of NEC among infants with SGA (19). Redistribution of blood flow with a resultant reduction of blood flow to the splanchnic arteries is thought to be some of the mechanisms that increase the risk of NEC in growth-restricted infants (29).

Infants with SGA in our study were more prone to developing late-onset neonatal sepsis. Troger et al. had similar findings and this was elucidated by the increased use of central venous catheters and a longer time to reach enteral feeds in the SGA population (30). Previous studies have noted thymic atrophy, as well as lymphopenia and deficiencies in humoral responses, in infants with SGA as additional potential mechanisms related to LOS (31).

As more premature infants survive due to improved neonatal care, the incidence of ROP has been increasing and South Africa has become a part of the third epidemic of ROP (32). Bhoghossian et al. (19) in the VON United States study and Tsai et al. (20) in Taiwan found an increased risk of ROP among infants with SGA. We did not find a statistically significant risk of ROP in our SGA babies. This may be explained by the small numbers of infants who were screened as the screening program for ROP only started in 2015 at GSH.

A limitation of this study is that only 30–40% of infants in our institution have an early ultrasound scan (<20 weeks' gestation). When an early ultrasound was not available, Ballard score or postnatal foot length was used to estimate gestational age, which may be less accurate by up to 2 weeks (33). Other limitations include that our study was a single-site hospital study hence it may not be generalized to all resource-limited settings. We also only looked at in-hospital mortality and yet the associations of SGA may be long term. This study is one of the very few studies to report on outcomes of SGA VLBW outcomes in a middle-income country. The study was done in a tertiary setting with high volumes of VLBW. We used the VON database with standard data definitions adapted to harmonize with institutional guidelines in management.

Conclusion

Groote Schuur Hospital, a public academic hospital in a middle-income country, had a 12.7% rate of infants with SGA VLBW, higher than often reported in high-income countries.

Infants with SGA VLBW at GSH had approximately two times the risk of mortality as compared to their AGA counterparts and increased morbidities. These findings are useful for perinatal decision-making and counseling of parents.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town (R117/2020). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

MM was responsible for designing the study proposal, writing the protocol and report, interpreting results, and looking up references. DE was responsible for designing the study proposal, editing the protocol and report, interpreting results, and updating reference list. EE was responsible for designing the study proposal, analyzing the data, designing tables and figure, and editing the report and references. NR was responsible for designing the study proposal and editing the report. LT was responsible for designing the study proposal, editing the protocol and report, interpreting results, designing **Figure 1**, and updating references. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Susan Coffin,
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University of Ilorin, Nigeria
Marcia Mangiza,
Ministry of Health and Child Care,
Zimbabwe

*CORRESPONDENCE
Dagnew Getnet Adugna
dagnewgetnet5@gmail.com

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Maternal and neonatal factors associated with low birth weight among neonates delivered at the University of Gondar comprehensive specialized hospital, Northwest Ethiopia

Dagnew Getnet Adugna* and Misganaw Gebrie Worku

Department of Human Anatomy, School of Medicine, College of Medicine and Health Science, University of Gondar, Gondar, Ethiopia

Introduction: Low birth weight is a major contributory factor to infant mortality. Although low birth weight remains an important public health problem in Ethiopia, little emphasis is paid to its intervention as a means of reducing neonatal mortality. The aim of this study was to assess the magnitude of low birth weight and its associated maternal and neonatal factors in newborns delivered at the University of Gondar Comprehensive Specialized Hospital.

Methods: Hospital-based cross-sectional study was conducted, and 481 study participants were selected using systematic random sampling methods. Pre-tested interviewer-administered questionnaires were used to collect the data. Bivariable and multivariable binary logistic regression was implemented. Finally, the odds ratio with a 95% CI and a *p*-value of <0.05 were used to identify factors associated with low birth weight.

Result: The prevalence of low birth weight was 12.5% (95% CI; 9.8, 15.7%). Preterm birth (AOR = 38; 95% CI: 15.3, 93.0), pregnancy-induced hypertension (PIH) (AOR = 2.6; 95%CI: 1.1, 6.4), maternal body mass index (BMI) of < 18.5 kg/m^2 (AOR = 6.8; 95% CI: 1.5, 31.1), and grand multiparity (AOR = 4.2; 95% CI: 1.2, 16) were factors positively associated with low birth weight. However, babies delivered from mothers with age > 35 years (AOR = 0.14:95% CI 0.03, 0.7) had lower odds of low birth weight.

Conclusion: In this study, the prevalence of low birth weight was higher than in the previous studies. The study revealed preterm birth, PIH, BMI of < 18.5 kg/m^2, and grand multiparity were independent factors that increase the low birth weight while maternal age > 35 years reduces the low birth weight. Therefore, healthcare professionals should emphasize the early identification and management of women with PIH, tackling prematurity, and preventing maternal malnutrition through nutritional counseling as much as possible.

KEYWORDS

low birth weight, prevalence, birth weight, newborns, factors, Ethiopia

Introduction

Birth weight is vital to the growth and developmental capacity of the infant, which is an important factor for child survival, disabilities, and stunting (1). Low birth weight often has long-term negative effects on the onset of chronic diseases in the course of life and thus needs effective public health measures (2). The WHO describes low birth weight as a birth weight of <2,500 g regardless of the gestational age, and it continues to be a major public health issue globally with several short and long-term adverse outcomes (3). Low birth weight incorporates both premature births (a birth of newborns before 37 weeks of gestation) and small for gestational age (birth weights less than 10th percentile for newborns of the same gestational age) (4–6). It can be caused by premature birth or the neonate being small for gestational age or both (5). It is a major underlying contributor to neonatal and infant mortality, which is responsible for almost half of all perinatal deaths (7). Globally, 15 to 20% of newborns have low birth weight, affecting more than 20 million births each year (1, 3, 8, 9). In Africa, the prevalence of low birth weight varies from 6.3 to 25.5% (10–13). In Ethiopia, the magnitude of low birth weight varied greatly ranging from 7.8 to 54% (14–18). The WHO has noted that most low birth weight neonates are delivered in developing countries; of these, 90% of them were in sub-Saharan Africa (19). Low birth weight remains the main public health concern due to poverty and other social factors such as lower socioeconomic level, lack of nutrition, and prenatal care (20). Factors that may raise the risk of developing low birth weight in addition to premature birth and intrauterine growth retardation (IUGR) include infection during pregnancy, inadequate weight gain, previous pregnancy with a low birth weight infant, smoking, alcohol or drug use, and age of the mother (21–23). In 2012, World Health Assembly's global nutrition goal planned to decrease the prevalence of LBW by 30% between 2012 and 2025 (24). The first important step in designing effective management strategies is to recognize predictors of low birth weight. According to various studies, socio-demographic, obstetrics, and fetal factors are associated with low birth weight. This includes maternal age, multiple births, pregnancy-induced hypertension, obstetric complications, chronic medical disorders, and nutritional status (11, 25–30). Besides, the educational status of the partner, lack of antenatal care (ANC) visit, history of obstetric problems, maternal weight during pregnancy, short birth interval, and gravidity were factors significantly correlated with low birth weight (7, 8, 27, 31–37). This forecasts the future wellbeing, development, and viability of the child and is a strong overview of several public health concerns such as long-term maternal malnutrition and inadequate healthcare throughout pregnancy (31). Low birth weight is still an important public health concern in Ethiopia. However, in most developing countries, namely, Ethiopia, little emphasis is given to low birth weight intervention as a means of reducing neonatal mortality. Although there is some evidence of low birth weight in some parts of Ethiopia, there is a great discrepancy in the prevalence and factors that affect low birth weight in different geographical regions and periods. Also, most previous studies did not consider the methodological issue including appropriate sample size calculation and sampling technique. As a result, the study addresses this methodological gap which other studies did not consider (for instance, the previous study conducted in Gondar used a retrospective study with a small sample size of 240). Therefore, the aim of this study was to assess the magnitude of low birth weight and its associated maternal and neonatal factors at the University of Gondar comprehensive specialized hospital. The findings of this study may help policymakers, obstetric care providers, and program managers to design an intervention for preventing low birth weight.

Materials and methods

This study was conducted at the University of Gondar Comprehensive Specialized Hospital, Gondar town, Northwest Ethiopia. It is one of the largest teaching hospitals in Ethiopia, located in the Central Gondar zone of Amhara Regional State. It is found 750 km away from Addis Ababa, the capital city of Ethiopia, and is serving more than 7.5 million people living in the Central Gondar Zone and the neighboring zone. It is composed of operating rooms, maternity units, intensive care units (ICUs), a fistula center, 13 different inpatients wards, and outpatient departments. The maternity units of the hospital provide different services such as antenatal, delivery, and postnatal services to women in the reproductive-aged group (15–49 years). According to the hospital directors' annual reports, around 9,804 neonates were delivered at the University of Gondar Comprehensive Specialized Hospital in the year 2019/20. An institution-based prospective cross-sectional study was conducted from 1 March to 1 May 2020.

All maternal-newborn pairs, who have attended delivery at the University of Gondar Comprehensive Specialized Hospital, were the source population, and those maternal-newborn pairs who have attended delivery during the data collection period were the study population.

All neonates delivered at the University of Gondar Comprehensive Specialized Hospital during the study period were included. Twin newborns were excluded from the study.

The sample size was calculated using a single population proportion formula with the assumption of 11.6% proportion taken from a similar study in Ethiopia (38), considering a 95% confidence level and marginal error of 3%. By adding a 10% non-response rate the required sample size was 481. A systematic random sampling technique was used for the selection of study participants. The client registration book of 2 months before the data collection period was reviewed and then the total number of deliveries during a data collection time was calculated (1,634 delivery in 2 months). To calculate the sampling interval (K), the total estimated number of all births during the study period (1,634) was divided by the sample size (481). The sampling interval (K) was calculated as 1,634/481 = 3. Of the first three study participants, one was chosen randomly. Then, participants in every three intervals were included until the target sample size was achieved.

The dependent variable for this study was low birth weight (defined as a birth weight of newborns < 2,500 g). The independent variables are socio-demographic variables (maternal age, residence, religion, ethnicity, educational status, marital status, occupational status, and monthly income), maternal anthropometric factors (maternal height, weight, and BMI), obstetric- and medical-related factors (gestational age, PIH, parity, birth interval, utilization of ANC visit, birth interval, and chronic medical illness during pregnancy), and newborn factors (sex of the baby and neonatal death). Pregnancy-induced hypertension is defined as the presence of at least one of the following diseases: (A) previous hypertension, (B) gestational hypertension and pre-eclampsia, (C) previous hypertension and superimposed gestational hypertension with proteinuria (39).

To collect the required data, pretested interviewer-administered questionnaires were used. The questionnaire was developed and modified from different literature. It was written in English, converted into Amharic, and translated back into English for suitability and acceptance in approaching respondents. In addition, medical records were reviewed to obtain additional data about maternal and newborn factors. The data were collected by four professional midwives working in the labor wards of the hospital. Anthropometric measurements were done for newborns and mothers using a standard anthropometric technique. The birth weight of a neonate was measured within 1 h of birth using a beam balance scale. The weight of the mothers was measured using a weight measuring scale and recorded accurately to 100 g. Maternal height was measured with calibrated height measuring steel connected to the beam balance and recorded with an accuracy of 0.5 cm. Women were instructed to remain standing up in erect position, with their barefoot close together, while a horizontal headpiece was lowered onto the mother's heads. Then, maternal BMI was calculated accordingly. The last normal menstrual period was obtained from the mother's chart since most of the mothers had regular ANC follow-ups. Moreover, if the last

TABLE 1 Socio-demographic and anthropometric characteristics of mothers in the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2020 ($n = 481$).

Variables	Category	Frequency	Percent (%)
Maternal age (years)	≤20	29	6
	21–35	410	85.3
	>35	42	8.7
Residence	Urban	376	78.2
	Rural	105	21.8
Ethnicity	Amhara	466	96.9
	Tigrie	2	0.4
	Kimant	13	2.7
Marital status	Married	451	93.8
	Single	17	3.5
	Divorced and separated	13	2.7
Religion	Orthodox	437	90.8
	Muslim	44	9.2
Maternal education	Unable to read and write	88	18.3
	read and write only	39	8.1
	Primary Education	67	13.9
	Secondary education	119	24.7
	Diploma and above	168	34.9
Husband education	Unable to read and write	71	14.8
	read and write only	60	12.5
	Primary Education	63	13.1
	Secondary education	93	19.3
	Diploma and above	194	40.3
Maternal occupation	Housewife	230	47.6
	Government employee	123	25.8
	Non-government employee	8	1.7
	Merchant	91	18.9
	Daily laborer	11	2.3
	Students and unemployed	18	3.7
Monthly income in Ethiopian Birr	≤1210	51	10.6
	1211–8970	353	73.4
	>8970	77	16
Number of family members	≤4 members	373	77.5
	>4 members	108	22.5

normal menstrual period was not documented in the chart, mothers were interviewed during labor. An early pregnancy ultrasound report (≤20 completed weeks of gestation) was also used. Finally, gestational age was determined using either the last normal menstrual period or a chart review of early ultrasound results.

Data quality control

In total, 3 days of training were provided to data collectors on how to collect the data. Pre-testing of the questionnaire was conducted with 5% of mothers who were delivered in Debark hospital. Daily supervision of the data collectors was performed by the principal investigators. The collected data were checked for completeness and consistency before entry.

Data processing and analysis

The data were entered into Epidata version 4.6. Then, data were exported and analyzed using STATA version14 software. Descriptive statistics such as percentages, mean, and standard deviations (SD) were used to explain the characteristics of study participants. The findings were presented in the form of tables and text. A chi-square test was used to verify the assumptions. Variables that were passed at the chi-square test were selected for multiple logistic regression analyses. Bivariable and multivariable binary logistic regression analyses were carried out. In the bivariable analysis, variables with a *p*-value of < 0.2 were selected for multivariable binary logistic regression analysis. In the multivariable logistic regression analysis, adjusted odds ratios with corresponding 95% CIs were computed. Finally, variables with a *p*-value of < 0.05 were used to determine factors significantly associated with low birth weight. Model fitness was tested using the Hosmer–Lemeshow test (0.925). The multi-collinearity test between explanatory variables was assessed using variance influencing factor (VIF) and tolerance and the mean VIF was less than 5.

Results

Socio-demographic variables of the respondents

A total of 481 respondents were involved in this study with a response rate of 100%. The mean age of the mothers was 28.2 (SD ± 5.4) years. About 85.3% of the study participants were between the age of 21 and 35 years old. Most (96.9%) of the participants were Amhara and 90.8% of them were orthodox religious followers. The majority (93.8%) of respondents were married, and around 47.6% were housewives. Regarding educational status, nearly 35% of the mothers were diploma holders and above. Concerning the income distribution, 10.6% of the mothers had a monthly income of ≤ 1,210 Ethiopian birr (Table 1).

Anthropometric characteristics of mothers

In our study, majority (90.3%) of women had a height of >150 cm and nearly three-fourth (78.4%) of mothers had normal BMI (Table 2).

Obstetric and medical-related characteristics of mothers

In this study, the majority (95.6%) of the study participants had regular ANC follow-ups during pregnancy and 76.6% of them had at least four visits. Regarding the pregnancy status, the majority (72.6%) of pregnancies were wanted and planned. The majority of (88.2%) mothers had got dietary counseling by health professionals during their ANC follow-up period. Out of 481 mothers, 88.4% were term. One in ten mothers had a chronic medical illness during pregnancy (10%). Concerning the mode of delivery for current pregnancy, 54.1% of women were giving birth *via* spontaneous vaginal delivery (Table 3).

Neonatal characteristics

The mean birth weight of the newborns was 3,027 g (SD ± 584). The average gestational age of the neonates was 39 (SD ± 2) weeks. Out of the total number of poor Apgar score neonates (a score of < 7 at 5 min), 47.1% had low birth weight. Of the total number of birth defect neonates, 33.3% had low birth weight (Table 4).

Prevalence of low birth weight

The prevalence of low birth weight in this study was 12.5% (95% CI: 9.8, 15.7%). About 45% of the low birth weight neonates were preterm (<37 weeks of gestation).

TABLE 2 Anthropometric measurement characteristics of the mother in the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2020 (*n* = 481).

Variables	Category	Frequency	Percent (%)
Height (cm)Weight (kg)	≤150	42	8.7
	>150	439	91.3
	<50	44	9.2
Maternal BMI(kg/m2)	≥50	437	90.8
	<18.5	15	3.1
	18.5–22.99	377	78.4
	≥25	89	18.5

TABLE 3 Obstetric and medical-related characteristics of the mother in the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2020 (n = 481).

Variables	Category	Frequency	Percent (%)
ANC follow up	Yes	460	95.6
	No	21	4.4
Number of ANC visit	<4 visits	107	23.3
	≥4 visits	353	76.7
Pregnancy status	Wanted and planned	349	72.6
	Wanted but unplanned	114	23.7
	Unwanted and unplanned	18	3.7
Dietary counseling during pregnancy	Yes	424	88.2
	No	57	11.8
Parity	Primiparous	181	37.6
	Multiparous	260	54.1
	Grand multiparous	40	8.3
Gestational age at delivery	Preterm	40	8.3
	Term	425	88.4
	Post-term	16	3.3
Birth interval in year	<3	246	51.1
	≥3	235	48.9
Pregnancy-induced hypertension	Yes	54	11.2
	No	427	88.8
Meal frequency per day	<4 times	269	55.9
	≥4 times	212	44.1
Medical illness	Yes	48	10
	No	433	90
Types of medical illness	HIV/AIDS	5	10.4
	Anemia	20	41.7
	Urinary tract infection	8	16.7
	Cardiac disease	3	6.2
	Others*	12	25
Previous history of stillbirth	Yes	42	8.7
	No	439	91.4
Modes of delivery	Spontaneous vaginal delivery	260	54.1
	Cesarean section	205	42.6
	Instrumental delivery	16	3.3

Others* = renal disease and malaria.

Factors associated with low birth weight

Variables including, sex of the newborn, Apgar score, birth interval, congenital malformation, and chronic medical illness were excluded from multivariable analysis because their p-value in the bivariable analysis was > 0.2. In the multivariable logistic regression analysis: Maternal age of > 35 years, preterm birth, PIH, maternal BMI of < 18.5 kg/m^2, and grand multiparity were statistically associated with low birth weight. In this study, mothers who deliver after the age of 35 years had 86% lower odds of low birth weight babies than those mothers between 21 and 35 years old (AOR = 0.14; 95% CI: 0.03,0.7). The odds of being low birth weight in babies born from mothers who gave preterm birth were 38 times greater than low birth weight in babies from those mothers who gave birth ≥ 37 weeks of gestation (AOR = 38; 95% CI: 15.3,93). Mothers with PIH had 2.6 times higher odds of giving low birth weight babies than their counterparts (AOR = 2.6; 95% CI; 1.1, 6.4). The odds of being low birth weight in babies born from mothers whose BMI was less than 18.5 kg/m^2 were 6.8 times higher than the odds of low weight in babies from mothers with a BMI of > 25 kg/m^2 (AOR = 6.8; 95% CI: 1.5, 31.1). The odds of being low birth weight in neonates born from grand multiparous women were four times higher than the odds of low birth weight in neonates from multiparous women (AOR = 4.2; 95% CI:1.2,16) (**Table 5**).

TABLE 4 Neonatal-related variables with the prevalence of low birth weight in the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2020 (n = 481).

Variables	Category	Low birth weight		Total
		Yes	No	
Sex newborn	Male	35(12.9%)	236(87.1%)	271(100%)
	Female	25(11.9%)	185(88.1%)	210(100%)
Neonatal death	Yes	5(41.7%)	7(58.3%)	12(100%)
	No	55(11.7%)	414(88.3%)	469(100%)
APGAR score	Poor (<7)	16(47.1%)	18(52.9%)	34(100%)
	Good (≥7)	44(9.8%)	403(90.2%)	447(100%)
Congenital malformation	Yes	1(33.3%)	2(66.7%)	3(100%)
	No	60(12.5%)	418(87.5%)	478(100%)

APGAR: Appearance, pulse rate, grimace, activity, respiratory rate.

Discussion

In this study, the overall prevalence of low birth weight was 12.5% [95% CI: 9.8, 15.7%] which is in agreement with the study conducted in Dangla (14) and the worldwide prevalence of low birth weight (24). The prevalence of low birth weight in this study is lower than the reports in Wolaita Sodo, Ethiopia (1), Kersa, Ethiopia (15), and India (9). The variation in the prevalence of low birth weight among different studies might be explained because of variation in methodology, study setup, study time, and study design. The difference between the present study and the Wolaita Sodo report might be due to the variation in methodology, in the way that, the current study considered only singleton deliveries which decrease the burden of low birth weight. The difference in

TABLE 5 Factors associated with low birth weight among newborns delivered at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2020 (n = 481).

Variables	Category	Low birth weight Yes (%)	Low birth weight No (%)	COR (95% CI)	AOR (95% CI)
Maternal age (years)	≤20	7 (11.7%)	22 (5.2%)	2.3 (0.9,5)	2.8(0.8, 9.7)
	21–35	50 (83.3%)	360 (85.5%)	1	1
	>35	3 (5%)	39 (9.3)%	0.6 (0.1, 0.9)	0.14(0.03, 0.7)*
Residence	Urban	41 (68.3%)	335(79.6%)	1	1
	Rural	19 (36.7%)	86(20.4%)	1.8 (0.9, 3)	0.7(0.2, 1.8)
Maternal education	Unable to read and write	20(33.3%)	68(16.2%)	3.2(1.5, 6.7)	2.5(0.7, 8.5)
	read and write only	5 (8.3%)	34 (8%)	1.6 (0.5,4.8)	0.8(0.2,3.4)
	Primary Education	8 (13.4%)	59(14%)	1.4 (0.6,3.8)	0.8(0.3,2.6)
	Secondary education	13 (21.7%)	106(25.2%)	1.3 (0.6,3.9)	1(0.4,2.9)
	Diploma and above	14 (23.3%)	154(36.6%)	1	1
Monthly income in Ethiopian Birr	≤1210	10 (16.7%)	41(9.7%)	4.4(1.3,15)	1.9(0.3,10)
	1211–8970	46 (76.6%)	307(72.9%)	2.7(0.9,7.8)	1.5(0.4,5.6)
	>8970	4 (6.7%)	73(17.4%)	1	1
ANC visit	Yes	55 (9.7%)	405(96.2%)	1	1
	No	5 (8.3%)	16(2.8%)	2.3(0.8,6.5)	1.5(0.3,6.7)
Pregnancy status	Wanted and planned	38 (63.3%)	311(73.9%)	1	1
	Wanted but unplanned	19 (31.7%)	95(22.6%)	1.6(0.9,2.9)	0.9(0.4,2.2)
	Unwanted and unplanned	3 (5%)	15(3.5%)	1.6(0.5,5.9)	1 (0.2,4.9)
Parity	Primiparous	27(45%)	154(36.6%)	1.6(0.9,2.9)	1.9(0.8,4.4)
	Multiparous	25(41.7%)	235(55.8%)	1	1
	Grand multiparous	8(13.3%)	32 (7.6%)*	2.4(1.01,5.9)	4.2(1.2,16)*
Gestational age (weeks)	<37	27(45%)	13(3.1%)	25 (12,54)	38(15.3,93.0)**
	≥37	33(55%)	408(96.9%)	1	1
PIH	Yes	12(20%)	42(10%)	2.3(1.2,4.6)	2.6(1.1,6.4)*
	No	48(80%)	379(90%)	1	1
Meal frequency per day	<4 times	42(70%)	227(53.9%)	2(1.1,3.5)	1.4(0.6,3.1)
	≥4 times	18(30%)	194(46.1%)	1	1
Maternal BMI (kg/m2)	<18.5	6(10%)	9(2.1%)	5.9(1.7,20)	6.8(1.5,31.1)*
	18.5–22.99	45(75%)	332(78.9%)	1.2(0.6,2.5)	0.9(0.3,2.5)
	≥25	9(15%)	80(19%)	1	1
Neonatal death	Yes	5(8.3%)	7(1.7%)	5.4(1.7,17.5)*	2.4 (0.4,14)
	No	55(91.7%)	414(98.3%)	1	1

*Statistically significant at $p < 0.05$, ** $p < 0.001$.
The Hosmer–Lemeshow test of goodness-of-fit = 0.925.
1, reference category.

the study set-up may have been a reason for variations since the present study was carried out in an urban area, whereas the study done in Kersa was in a rural area. Besides, the possible explanation for this variation is also the time difference between the studies. There is a 10-year time gap between the present study and the study done in Kersa, Ethiopia. Thus, increasing healthcare coverage and quality of care over time may result in a reduction in low birth weight. The other reason for variation may be the study design. For example, the Indian study was a community-based study, but the present study is a hospital-based one, particularly, in healthcare facilities. Women who were delivered in healthcare facilities are assumed to obtain regular ANC follow-up and good interventions, which drastically decrease low birth weight (29, 40).

In the current study, the prevalence of low birth weight infants was higher than in the studies conducted in Jimma (20), Ghana (2), Axum (25), and Yazd, Iran (41). The possible explanation for this variation might be due to a difference in the nutritional status of women and the healthcare provider's commitment to ANC service provision, particularly on the nutritional counseling during pregnancy (1). In addition, the variation between the present study and a study done in Iran might be due to differences in socio-demographic factors, health service delivery system, and the approaches to managing women during the ANC follow-up period.

In the multivariable binary logistic regression analysis parity, maternal age, gestational age, pregnancy-induced hypertension, and maternal BMI were significantly associated with low birth weight. Mothers who deliver after the age of 35 years had lower odds to have a low birth weight baby which is similar to other studies (2, 11, 37). This might be because higher age groups might be less likely to deliver low birth weight infants usually as the pregnancy might be planned and wanted, which leads to giving more attention to the dietary value and healthcare services utilization and increased awareness of pregnancy's danger signs and main risk factors (37). In this study, grand multiparous women had higher odds to deliver low birth weight infants. This study is supported by the finding conducted in Jimma (20), Wolaita Sodo (1), East Gojam (27), and Ghana (11). This can be justified by grand multiparty mothers are at high risk of several adverse fetal and maternal outcomes such as abnormal implantation, abruption placenta, instrumental delivery, postpartum hemorrhage, preterm birth, and neonatal and maternal admission to intensive care unit, some of which may have an effect on fetal development including their birth weight (42). Besides, the odds of women who gave birth before 37 weeks of gestation had greater odds to deliver a low birth weight infant. The finding was in line with the studies carried out in Dangla (14), Jimma (20), Addis Ababa (31), and Tigray region (25). The possible explanation for this is as the gestational age of the fetus falls under the acceptable range of time, the birth weight of the fetus decreased significantly because of the premature birth (25). Interestingly, women having pregnancy-induced hypertension had higher odds of low birth weight delivery, which is consistent with the studies done in Wolaita Sodo (1), East Gojam (27), and Addis Ababa (31). This might be due to a reduction in uteroplacental blood perfusion as a result of vasoconstriction of blood vessels during a hypertensive state, which leads to intrauterine growth restriction and premature birth which becomes low birth weight (27, 43). Regarding the maternal BMI, those women who had a BMI of < 18.5 kg/m2 were more likely to give low birth weight infants. This is in agreement with studies conducted elsewhere (32, 37, 44). This might be because maternal BMI is one of the main parameters to assess nutritional status. Those mothers who had a BMI of less than 18.5 kg/m^2 indicate the presence of under-nutrition that shows chronic malnutrition in adults. This might result in the impairment of fetal growth and development in the uterus. Therefore, low birth weight might easily occur. Malnutrition in pregnancy has also been related to decrease placental weight and surface area, which might restrict the transport of nutrients from the placenta to the fetus. Furthermore, poor maternal nutrition leads to a decrement in serum levels of hormones, such as leptin and estrogen, that results in fetal growth restriction (37).

As the study design was cross-sectional, we did not determine the reverse causality between the dependent and different independent variables, and this is one of the main limitations of this cross-sectional study. The study did not assess some factors such as lifestyle factors (dietary habit, level of physical activity, etc.), intrauterine growth retardation, small for gestational age, and weight gain during pregnancy.

Conclusion

The prevalence of low birth weight in this study was higher than in previous studies, implying that it continues to be a major public health concern. This study showed that preterm birth, PIH, grand multiparity, and BMI of < 18.5 kg/m^2 were the major associated factors of low birth weight. However, maternal age > 35 years was a protective factor. Therefore, early identification and management of women with PIH, tackling prematurity, and preventing maternal malnutrition through nutrition education during the ANC follow-up period are recommended to reduce the burden of low birth weight.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical review board University of Gondar. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

DA and MW: conceptualization, formal analysis, methodology, resources, software, supervision, validation, visualization, and writing—original draft. DA: data curator and investigation. Both authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ju Lee Oei,
University of New South Wales,
Australia

REVIEWED BY
Fielding Bruder Stapleton,
University of Washington, United States
Ruth Gottstein,
Manchester University NHS Foundation
Trust (MFT), United Kingdom

*CORRESPONDENCE
Changyi Yang
neo595@163.com
Zhankui Li
13772151229@163.com

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work

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Discharge against medical advice among infants with 24–31 weeks' gestation admitted to Chinese neonatal intensive care units: A multicenter cohort study

Wenlong Xiu[1†], Ruimiao Bai[2†], Xinyue Gu[3], Siyuan Jiang[3,4], Baoquan Zhang[1], Ya Ding[2], Yanchen Wang[3], Ling Liu[5], Jianhua Sun[6], Yun Cao[3,4], Wenhao Zhou[3,4], Shoo K. Lee[7,8], Zhankui Li[2*‡] and Changyi Yang[1*‡] on behalf of the Chinese Neonatal Network

[1]Department of Neonatology, Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou, China, [2]Department of Neonatology, Northwest Women's Children's Hospital, Xi'an, China, [3]NHC Key Laboratory of Neonatal Diseases (Fudan University), Children's Hospital of Fudan University, Shanghai, China, [4]Department of Neonatology, Children's Hospital of Fudan University, Shanghai, China, [5]Department of Neonatology, Guiyang Maternal Child Health Care Hospital, Guiyang, China, [6]Department of Neonatology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [7]Maternal-Infant Care Research Centre and Department of Pediatrics, Mount Sinai Hospital, Toronto, ON, Canada, [8]University of Toronto, Toronto, ON, Canada

Background: Previous studies demonstrated high rates of discharge against medical advice (DAMA) among very preterm infants (VPIs) in China.

Objectives: The aim of this study was to investigate the concurrent incidence, variation, and predictors of DAMA, along with the effect of DAMA on mortality of VPIs in China using data from the Chinese Neonatal Network (CHNN).

Methods: All infants born at 24–31 completed weeks' gestation and admitted to 57 CHNN neonatal intensive care units (NICUs) in 2019 were included for this cohort study, excluding infants with major congenital anomalies. Patient information was prospectively collected using the CHNN database. Multivariable log-linear regression analysis was used to assess the association of perinatal factors and DAMA.

Results: A total of 9,442 infants born at 24–31 completed weeks' gestation and admitted to 57 CHNN participating sites in 2019 were included in the study. Overall, 1,341 infants (14.2%) were discharged against medical advice. Rates of DAMA decreased with increasing gestational age (GA), and infants with lower GA were discharged earlier. DAMA infants had significantly higher rates of necrotizing enterocolitis, severe brain impairment, and bronchopulmonary dysplasia than non-DAMA infants. A total of 58.2% DAMA infants were predicted to die after discharge. The attributable risk percentage of mortality among DAMA infants was 92.4%. Younger maternal age, lower gestational age, small for gestational age, and Apgar score ≤3 at 5 min were independently associated with an increased risk of DAMA, while infants with antenatal steroids were less likely to be DAMA.

Conclusion: The rate of DAMA in preterm infants between 24 and 31 weeks' gestation remained high in China with a significant impact on the mortality rates. Continuous efforts to reduce DAMA would result in substantial improvement of outcomes for VPIs in China.

KEYWORDS

discharge against medical advice, preterm infants, mortality, morbidity, risk factor

Introduction

Infants born at less than 32 weeks (very preterm infants, VPIs) account for about 15–16% of all preterm births, with the highest mortality and morbidity rates (1, 2). In China and many other middle- or low-income countries, it has been reported that discharge against medical advice (DAMA) contributes significantly to the high mortality and morbidity of VPIs (3–8). DAMA refers to a situation wherein parents terminate treatment before the treating physicians recommend discharge. With limited physiological reserve of VPIs, they are at a very high risk of adverse outcomes in morbidity and mortality after DAMA (3, 4). Previous literature demonstrated that 70% of VPIs died following DAMA in China (9). Therefore, it is essential to collect detailed and high-quality data on DAMA of VPIs in China and to explore possible modified practices, aiming to reduce DAMA and improve overall outcomes of VPIs.

The Chinese Neonatal Network (CHNN) is a national collaborative research network focusing on neonatal and perinatal clinical studies in China (10). Established in 2018, CHNN has been maintaining a standardized database for all VPIs or very low birth weight infants admitted to NICUs across China from 1 January 2019. The objective of this study was to investigate the incidence, site variation, and predictors of DAMA, along with the impact of DAMA on mortality of VPIs in China using data from the CHNN.

Materials and methods

Study setting

This cohort study used the prospectively collected data from CHNN database. A total of 57 tertiary hospitals from 25 provinces and municipalities across China collected the whole year data using CHNN database in 2019, including all three national medical centers of children, all five regional medical centers of children, 30 provincial perinatal or children's medical centers, and 19 major referral centers in large cities across China. Notably, 43 hospitals were perinatal centers with delivery facilities, and 14 hospitals were free-standing children's hospitals. The ethics review board approved this study of Children's Hospital of Fudan University (No. 2018-296), which all participating hospitals recognized. Waiver of consent was granted at all sites because of de-identified patient data.

The incidence of preterm birth in China was about 7.04% in 2015–2016 (11), with approximately 160,000 VPIs born in China each year (2). Therefore, CHNN database covered around 5% of VPIs who were born in China. VPIs not included in the database were either admitted to other NICUs or lower-level units, or not admitted to NICUs for treatment. Therefore, our data only represent outcomes of VPIs who received the highest level of care in major tertiary NICUs in China.

Study design and population

All infants born at 24–31 completed weeks' gestation and admitted to CHNN-participating neonatal intensive care units (NICUs) between 1 January 2019 and 31 December 2019 were eligible for this study. Infants with major congenital anomalies were excluded. Stillborn, delivery room deaths, moribund neonates on admission, and infants transferred to non-participating hospitals within 24 h after birth were not captured by the CHNN database. Re-admissions and transfers between participating hospitals were tracked as data from the same infants. Infants were followed until death or discharge.

Data collection

Patient information was abstracted from patient charts by trained personnel using predefined standard definitions. Data were directly entered into a customized data entry program with built-in error checking. Data were subsequently sent electronically to the CHNN coordinating center located at the National Children's Medical Center in Children's Hospital of Fudan University in Shanghai, with patient identity kept confidential. Site investigator was responsible for data quality control in each site. The coordinating center checked data for quality and completeness and conducted audits to ensure the quality of data (12).

Exposure

Discharge against medical advice, which is the exposure, was defined as when parents terminated treatment before the treating physicians recommended discharge according to discharge criteria in participating NICUs.

Outcomes

Outcomes included mortality (primary outcome) and the five major neonatal morbidities, including necrotizing enterocolitis (NEC), severe brain injury, sepsis, bronchopulmonary dysplasia (BPD), and severe retinopathy of prematurity (ROP).

We did not follow up the DAMA infants after discharge and there were no other reliable sources of the information on the outcome of these infants. Therefore, we used predefined criteria to predict the likelihood of death for DAMA infants (13). If infants required invasive or non-invasive mechanical ventilation, inotropes infusion, or total parenteral nutrition (no enteral feeds initiated) on the day of discharge, we considered that they would not survive after discharge.

For morbidities, NEC was defined as stage ≥2 according to Bell's stage (14, 15). Severe brain impairment was defined as degree ≥3 intraventricular hemorrhage (IVH) or cystic periventricular leukomalacia (cPVL). The diagnosis of severity of IVH was according to Papile's criteria (16). cPVL was defined as the presence of periventricular cysts on cranial ultrasound or magnetic resonance imaging. Sepsis was defined as positive blood or cerebrospinal fluid culture (17). BPD was defined as ventilation or oxygen dependency at 36 weeks' corrected age or at discharge, transfer, or death before 36 weeks (18). Severe ROP was defined as ROP stage III or above.

Covariable definitions

Gestational age (GA) was determined using the hierarchy of best obstetric estimate based on prenatal ultrasound, menstrual history, obstetric examination, or all three. If the obstetric estimate was not available or was different from the postnatal pediatric estimate of gestation by more than 2 weeks, the GA was estimated using the Ballard score (19). Small for gestational age (SGA) was defined as birth weight <10th percentile for the GA according to the Chinese neonatal birth weight values (20). Prenatal care was defined as at least one pregnancy-related hospital visit during pregnancy. Antenatal steroids were defined as partial or complete courses of antenatal corticosteroids before birth.

Statistical analysis

We described demographic characteristics by DAMA and non-DAMA group and provided crude risk ratios with 95% confidence interval to show the observed association between characteristics and DAMA. Kaplan–Meier curves were used to show the probability of non-DAMA over time after birth, while log-rank tests were applied to examine whether the probabilities were significantly different across GA groups. The Cochran–Armitage trend test was applied to examine the significance of the association between rate of DAMA and GA, and Jonckheere–Terpstra trend test was applied to determine the association between the median age at DAMA and GA. Attributable risk percent (ARP) was calculated to show the percentage of neonatal mortality that is predicted to be related to DAMA.

Multivariable log-linear regression models were used to measure the independent association between DAMA and perinatal factors. The model accounted for the cluster effect of different sites by applying generalized estimating equations.

Missing data

The proportion of missing data were <10% for those variables included in the model and we believed that the data were not missing at random; therefore, we did not do multiple imputation. The data management and all statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, United States). All analysis is done by SAS 9.4 software.

Results

Rates of discharge against medical advice

During the study period, a total of 9,520 infants born at 24–31 completed weeks' gestation were admitted to 57 CHNN sites, and 78 patients were excluded for major congenital anomalies. Thus, 9,442 cases were finally included in our study (**Figure 1**).

Overall, 1,341 infants (14.2%) were discharged against medical advice (**Figure 1**). Rates of DAMA decreased with increasing GA (**Table 1**). DAMA rates reached the peak of 43.5%

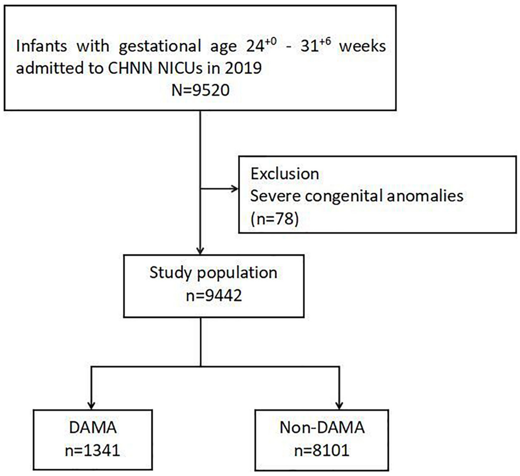

FIGURE 1
Study population. CHNN, Chinese Neonatal Network; DAMA, discharge against medical advice; NICU, neonatal intensive care unit.

at the GA of 24 weeks, while there were still 10.0% of infants born at 31 weeks discharged against medical advice.

There was a huge variation of DAMA rates among different hospitals (**Supplementary Figure 1**). The range of DAMA rates among different hospitals was from 0 to 66.7% in 24–27 weeks infants, and 0.9–34.8% in 28–31 weeks infants.

Age at discharge against medical advice

The median age at discharge for DAMA infants was 16 (IQR: 4–41) days. Age at discharge decreased with decreasing GA (**Table 1** and **Supplementary Figure 2**). DAMA infants at 24 weeks were most likely to be discharged within 3 days after birth. In comparison, the majority of DAMA infants at 29–31 weeks were discharged after 14 days after birth.

Maternal and infant characteristics

Baseline characteristics are summarized in **Table 2**. Infants in the DAMA group had lower GA and lower birth weight than infants who received complete care. They were also more likely to be female and outborn. Their mothers were younger, less likely to have maternal diabetes, and premature rupture of membranes. They were less likely to receive antenatal steroids and antenatal antibiotics and be delivered by cesarean section, compared with the non-DAMA group. Infants in the DAMA group were more likely to be SGA and had low Apgar scores (≤3) at 5 min.

Morbidities and mortality among discharge against medical advice infants

Discharge against medical advice infants had higher rates of neonatal morbidities, including NEC, severe brain impairment, and BPD, compared with infants who received complete care (**Table 3** and **Supplementary Table 1**). Overall, 58.2% (781/1,341) of DAMA infants required at least one type of intensive treatment at the time of discharge; hence, they were predicted to die after discharge (**Supplementary Table 2**). The predicted mortality among DAMA infants was 80.5 and 48.4% for infants <28 and 28–31 weeks, which was significantly

TABLE 1 Rates of discharge against medical advice among infants born at 24^{+0}–31^{+6} weeks' gestation in Chinese NICUs by gestational age.

Gestational age (weeks)	Total number of infants	DAMA, *n* (%)*	Age at DAMA, *n* (%)+			
			Median (IQR)	≤3 days	4–14 days	>14 days
24	92	40 (43.5)	3 (1.5, 8.5)	21 (52.5)	12 (30.0)	7 (17.5)
25	228	67 (29.4)	6 (2, 20)	26 (38.8)	19 (28.4)	22 (32.8)
26	449	125 (27.8)	7 (1.5, 30.5)	50 (40.3)	29 (23.4)	45 (36.3)
27	837	178 (21.3)	11 (3, 51)	48 (27.0)	48 (27.0)	82 (46.0)
28	1,415	233 (16.5)	14 (3, 54)	68 (29.4)	48 (20.8)	115 (49.8)
29	1,763	202 (11.5)	22 (5, 46)	42 (20.9)	40 (19.9)	119 (59.2)
30	2,153	245 (11.4)	28.5 (7, 40.5)	37 (15.2)	45 (18.4)	162 (66.4)
31	2,505	251 (10.0)	20 (8, 35)	35 (14.0)	73 (29.2)	142 (56.8)
Total	9,442	1,341 (14.2)	16 (4, 41)	327 (24.5)	314 (23.5)	694 (52.0)

*Cochran–Armitage trend test for DAMA rate among GA group, as well as Jonckheere–Terpstra trend test for median age at DAMA among GA group, both have a significant *p*-value < 0.01.
+Six infants have missing value on their birth date, so that we cannot calculate their age at DAMA.

TABLE 2 Baseline characteristics among infants born at 24^{+0}–31^{+6} weeks' gestation in China by DAMA and non-DAMA group.

	DAMA (*N* = 1,341)	Non-DAMA (*N* = 8,101)	Crude risk ratio (95% CI)
Maternal characteristics			
Maternal age, years, mean (SD)	29.9 (5.2)	31.0 (4.9)	0.96 (0.95, 0.97)*
Primigravida	655/1327 (49.4)	4,100/8,049 (51.0)	0.95 (0.86, 1.05)
Prenatal care	1,257/1,272 (98.8)	7,753/7,833 (99.0)	0.88 (0.55, 1.41)
Maternal hypertension	228/1,297 (17.6)	1,516/7,965 (19.0)	0.92 (0.80, 1.05)
Maternal diabetes	187/1,292 (14.5)	1,397/7,952 (17.6)	0.82 (0.71, 0.95)
Premature rupture of membranes	705/1,245 (56.6)	4,557/7,589 (60.1)	0.89 (0.80, 0.98)
Antenatal antibiotics	440/1,066 (41.3)	3,137/6,791 (46.2)	0.84 (0.75, 0.94)
Antenatal steroids	736/1,156 (63.7)	5,711/7,355 (77.7)	0.56 (0.50, 0.63)
Cesarean delivery	597/1,335 (44.7)	4,558/8,059 (56.6)	0.67 (0.60, 0.74)
Infant characteristics			
Gestational age, weeks, median (IQR)	29.0 (27.6, 30.6)	30.0 (28.6, 31.0)	0.81 (0.79, 0.84)*
Birth weight, grams, mean (SD)	1,208.5 (340.0)	1,343.0 (311.0)	0.89 (0.87, 0.90)*+
Small for gestational age	123/1,341 (9.2)	5,18/8,101 (6.4)	1.39 (1.17, 1.64)
Outborn	539/1,341 (40.2)	2,883/8,101 (35.6)	1.18 (1.07, 1.31)
Female	614/1,341 (46.0)	3,472/8,101 (42.9)	1.11 (1.01, 1.23)
Multiple birth	397/1,341 (29.6)	2,427/8,101 (30.0)	0.99 (0.88, 1.10)
Apgar score ≤3 at 5 min	38/1,216 (3.1)	77/7,626 (1.0)	2.45 (1.88, 3.19)

DAMA, discharge against medical advice; SD, standard deviation; IQR, interquartile range.
The denominator for certain rate is the number of infants with certain medical record, which means some data have missing values; DAMA was set as an event, while non-DAMA was set as a control.
*Mean risk ratio for continuous variables, with 1-unit increase if not specified (ratio between probability of observing event = 1 when exposure = $x + 1$ over exposure = x).
+With 100-unit (gram) increase.

higher than the observed mortality among infants who received complete care (14.2 and 6.4%, respectively) (**Table 4**).

Overall, the attributable risk percentage of mortality was 92.4% among DAMA VPIs. The attributable risk percentage of DAMA on mortality increased with advancing GA (**Table 4**).

Risk factors for discharge against medical advice

Younger mother, lower GA (24–28 weeks), SGA, and Apgar score ≤3 at 5 min were independently associated with an increased risk of DAMA. Infants who received antenatal steroids were less likely to be DAMA (**Table 5**).

Discussion

To the best of our knowledge, our report is the largest and latest nationwide study focusing on DAMA of VPIs in China. We identified a high rate of DAMA and substantial variation among different hospitals among VPIs in China. DAMA infants had high rates of severe brain impairment, BPD, and NEC, and showed a significant impact on mortality of VPIs. Younger maternal age, lower GA, SGA, and Apgar score ≤3 at 5 min were independently associated with an increased risk of DAMA, while antenatal steroids were associated with a decreased risk of DAMA.

Previous studies indicated near 21% of neonates with respiratory failure were DAMA in China in 2007–2008 (6–8). Jiang reported that the incidence of DAMA among VPIs in China was 19.7% in 2015–2016 and 13.3% in 2015–2018 (3, 13). Given the observed 14.2% DAMA rates among VPIs in our study, it has to be acknowledged that the rate of DAMA in preterm infants between 24 and 31 weeks' gestation remained high in China. Therefore, targeted efforts are definitely needed to reduce further or eliminate DAMA.

One improvement target may focus on infants with relatively larger GA. There were still 10–11% of infants born at 31 and 30 weeks discharged prematurely, resulting in high mortality for these infants. Given the large proportion of these infants among all VPIs admitted to Chinese NICUs, reducing DAMA rates among infants at 30–31 weeks will result in a significant reduction of the absolute number of DAMA.

The in-hospital mortality rate of VPIs with complete care in our research was close to that in developed countries, such as the Canada Neonatal Network (CNN) in the same period (4.4% in CHNN vs. 4.8% in CNN) (21). However, our data confirmed that the in-hospital mortality rates for VPIs in China should be interpreted with caution due to the high rate of DAMA and high mortality among DAMA infants. After taking DAMA infants into consideration, the overall mortality rates almost tripled. Also, DAMA infants showed higher rates of major neonatal morbidities. Therefore, when monitoring outcomes longitudinally or comparing outcomes regionally, nationally, or internationally, the DAMA infants should be taken into consideration to avoid overly optimistic estimates.

The attributable risk percentage of mortality was 92.4% among DAMA VPIs in our study, which means that 92.4% of deaths among DAMA infants might be related to the DAMA decision. However, these data should be interpreted with caution. In many instances, DAMA is likely to be motivated by a poor prognosis with regard to impending death or serious disability. Therefore, the overall attributable risk percentage of 92.4% might overestimate the proportion of deaths due to the DAMA decision. Anyhow, efforts to reduce DAMA rates will substantially decrease the mortality of VPIs in Chinese NICUs. Also, one cohort study estimated potential outcomes of DAMA among VPIs in China if they receive complete care based on outcomes of a group of propensity score matched non-DAMA infants. The studies found that 59% DAMA infants aged <32 weeks might have intact survival if intensive care services are provided (13).

Our data showed that infants with the youngest GA were mostly discharged within 3 days after birth, which indicated that parents tended to make an early decision of DAMA for infants with lower GA. Their discharge might be due to parents' concerns about the continuing suffering and grave outcomes, in terms of death or adverse neurodevelopmental outcomes. It probably reflected their lack of confidence in the chance of survival and outcome of infants born at lower GA

TABLE 3 Major neonatal morbidities among infants born at 24^{+0}–31^{+6} weeks' gestation in China by DAMA and non-DAMA group.

Morbidities	DAMA (*N* = 1,341)	Non-DAMA (*N* = 8,101)	Crude risk ratio (95% CI)
NEC stage II or above	91/1,341 (6.8)	401/8,101 (5.0)	1.32 (1.09, 1.61)
Severe brain impairment*	189/818 (23.1)	735/7,138 (10.3)	2.29 (1.97, 2.65)
IVH grade III or above	148/808 (18.3)	473/7,098 (6.1)	2.63 (2.25, 3.08)
cPVL	83/881 (9.4)	386/7,416 (5.2)	1.74 (1.41, 2.13)
Sepsis	107/1,341 (8.0)	752/8,101 (9.3)	0.87 (0.72, 1.04)
Early-onset sepsis	21/1,341 (1.6)	109/8,101 (1.4)	1.14 (0.77, 1.69)
Late-onset sepsis	88/1,071 (8.2)	658/7,948 (8.3)	0.82 (0.67, 1.00)
ROP stage III or above+	21/490 (4.3)	293/6,803 (4.3)	1.00 (0.65, 1.52)
BPD at corrected GA 36 week #	168/321 (52.3)	1,737/4,802 (36.2)	1.85 (1.50, 2.29)

NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.
The denominator for certain rate is the number of infants with certain medical record, which means some data have missing values; DAMA was set as an event, while non-DAMA was set as a control.
*Severe brain impairment is defined as severe IVH (grade 3 or 4) and/or cPVL, whose rate is calculated among infants with neuroimaging results.
+Rate of severe ROP is calculated among infants with ROP screening result.
#Rate of BPD is calculated among infants staying in NICU till their corrected GA reached 36 weeks.

TABLE 4 Neonatal mortality of DAMA and non-DAMA infants born at 24^{+0}–31^{+6} weeks' gestation in China.

Gestational age (weeks)	Overall death, *n/N* (%)	In-hospital death among non-DAMA, *n/N* (%)*	Predicted death among DAMA, *n/N* (%)+	ARP (95% CI), %#
24	61/92 (66.3)	23/52 (44.2)	38/40 (95.0)	53.5 (52.8, 54.1)
25	103/228 (45.2)	40/161 (24.8)	63/67 (94.0)	73.6 (73.1, 74.1)
26	137/449 (30.5)	39/324 (12.0)	98/125 (78.4)	84.7 (84.3, 85.0)
27	199/837 (23.8)	68/659 (10.3)	131/178 (73.6)	86.0 (85.7, 86.3)
28	216/1,415 (15.3)	72/1,182 (6.1)	144/233 (61.8)	90.1 (89.9, 90.4)
29	158/1,763 (9.0)	47/1,561 (3.0)	111/202 (55.0)	94.5 (94.3, 94.8)
30	140/2,153 (6.5)	34/1,908 (1.8)	106/245 (43.3)	95.9 (95.6, 96.1)
31	123/2,505 (4.9)	33/2,254 (1.5)	90/251 (35.9)	95.9 (95.7, 96.1)
Total	1,137/9,442 (12.0)	356/8,101 (4.4)	781/1,341 (58.2)	92.5 (92.4, 92.6)

*In-hospital death among non-DAMA are exactly based on medical record. Infants reported "Died" or "Palliative Care" were counted as death cases, while other situations were regarded as survival. Death among DAMA was defined as receiving intensive care at discharge, as shown in Table 4.
+Defined as requiring invasive or non-invasive mechanical ventilation, inotropes infusion, or total parenteral nutrition (no enteral feeds initiated) on the day of discharge.
#APR, attributable risk percent = [(p1 − p2)/p1] × 100 = [(Risk Ratio − 1) / Risk Ratio] × 100 (alternatively).

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both from parents and health providers. However, in recent decades, there have been major advances in the survival rate and outcome of infants with the smallest GAs in China (3, 10, 13). Obstetricians and neonatologists need to be aware of the latest data and inform families to make appropriate choices. For those infants with higher GA (29–31 weeks), their discharge might be associated with neonatal morbidities, which might be a serious blow for parents, giving most of them discharged after 14 days of life. Our data demonstrated that more infants in the DAMA group had severe brain impairment than the non-DAMA group, suggesting that fears for poor long-term outcomes might be one of the major reasons parents terminate the treatment of their babies. There were also more NEC and BPD in the DAMA group than in the non-DAMA group in VPIs. Therefore, more effort should be made to reduce those morbidities in VPIs. Our study also identified that perinatal factors, including low GA, SGA, younger mother, and low Apgar score at 5 min, were associated with an increased risk of DAMA, while antenatal steroids served as a protective factor for DAMA. Appropriate perinatal care may also contribute to the reduction of DAMA.

TABLE 5 Perinatal factors associated with DAMA among infants born at 24^{+0}–31^{+6} weeks' gestation in China.

Characteristics	Adjusted risk ratio (95% CI)#
Maternal characteristics*	
Maternal age, years+	0.97 (0.96, 0.98)
Maternal diabetes	0.90 (0.75, 1.08)
Premature rupture of membranes	0.90 (0.76, 1.07)
Antenatal steroids	0.70 (0.60, 0.83)
Cesarean delivery	0.93 (0.81, 1.06)
Infant characteristics*	
Gestational age, weeks	
24	4.83 (3.37, 6.92)
25	3.28 (2.32, 4.63)
26	3.13 (2.36, 4.16)
27	2.43 (1.90, 3.12)
28	1.79 (1.51, 2.14)
29	1.10 (0.93, 1.31)
30	1.18 (0.96, 1.44)
31	reference
Small for gestational age	1.76 (1.49, 2.07)
Outborn	1.11 (0.87, 1.41)
Female	1.09 (0.95, 1.24)
Apgar score ≤3 at 5 min	1.61 (1.12, 2.31)

NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.
Non-DAMA set as control.
*Those maternal and infant characteristics with *p*-value less than 0.05 in Table 2 are selected into the multivariate model, except for antenatal antibiotics and birth weight because of their collinearity with antenatal steroids and gestational age respectively.
+For maternal age as a continuous variable, odds ratios correspond to 1-year increase.
#The risk ratios (RR) and 95% CI were obtained by an extension of multivariable log-linear regression model, accounting for cluster effect of different sites by means of generalized estimating equations (GEE). The RR for each variable was adjusted for other variables listed in the table.

According to the published literature, besides concern about poor prognosis, the inability to afford the cost might also be a major reason for DAMA (22–24). However, increasing coverage of health insurance for neonates across China, change of one-child policy, and improving neonatal intensive care may result in changes in decision making of DAMA. Unfortunately, we did not collect information on the reasons for DAMA in our study. However, by recognizing this remaining problem, CHNN has launched targeted quality improvement initiatives aiming to reduce DAMA, with the first step as a prospective survey on specific DAMA reasons.

The development of neonatology and neonatal intensive care has been uneven among different districts in China. As found in our study, previous reports also showed significant variation of mortality and DAMA among VPIs in different hospitals in China (3, 4). Besides the variations in medical practice, there are various reasons for this wide variation of DAMA rates among different NICUs in China, which might include the sociocultural, socioeconomic, religious, and ethnic differences. Unfortunately, we did not collect this relevant information, so we were unable to perform a rigorous analysis of the causes of this variation. Recognizing these remaining problems, relevant studies organized by CHNN are underway. And a national network-level collaborative, a multifaceted quality improvement approach may be helpful to decrease the rate of DAMA *via* benchmarking, best-practice consensus, and sharing expertise.

Our study has several strengths. Our data were from the multicenter standardized database with clear definitions of variables and strict quality control, which reduced information bias. All participating NICUs were large tertiary centers representing the highest level of neonatal care in representing areas of China, which made the comparison of data reasonable. The large sample size enabled detailed stratification of GA, which can provide health providers and policymakers a more precise reference at each week of GA.

There were several limitations in our study. First, this is a hospital-based study instead of a population-based study. Delivery room deaths and live births without active resuscitation who were never admitted to NICUs were not included. This would result in an underestimation of the DAMA rate. Second, we did not actually follow up the DAMA infants after discharge, so we could not obtain an accurate mortality rate for these infants. Third, we could not identify specific reasons for DAMA and the causes of variability of DAMA rates among different NICUs because the database did not include such information.

Conclusion

Discharge against medical advice among VPIs has been decreasing over the past few years but remained high. DAMA had a significant impact on the mortality of VPIs in China. Continuous efforts to reduce DAMA would result in substantial improvement of outcomes for VPIs in China.

Members of the Chinese Neonatal Network

Chairmen: Chao Chen, Children's Hospital of Fudan University; Shoo K. Lee, Mount Sinai Hospital, University of Toronto. Vice-Chairmen: Lizhong Du, Children's Hospital of Zhejiang University School of Medicine; Wenhao Zhou, Children's Hospital of Fudan University. Site principle investigators of the Chinese Neonatal Network: Children's Hospital of Fudan University: Yun Cao; The Third Affiliated Hospital of Zhengzhou University: Falin Xu; Tianjin Obstetrics & Gynecology Hospital: Xiuying Tian; Guangzhou Women and Children's Medical Center: Huayan Zhang; Children's Hospital of Shanxi: Yong Ji; Northwest Women's and Children's Hospital: Zhankui Li; Gansu Provincial Maternity and Child Care Hospital: Jingyun Shi; Shengjing Hospital of China Medical University: Xindong Xue; Shenzhen Maternity and Child Health Care Hospital: Chuanzhong Yang; Quanzhou Women and Children's Hospital: Dongmei Chen; The Affiliated Suzhou Hospital of Nanjing Medical University: Sannan Wang; Guizhou Women and Children's Hospital/Guiyang Children's Hospital: Ling Liu; Hunan Children's Hospital: Xirong Gao; The First Bethune Hospital of Jilin University: Hui Wu; Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University: Changyi Yang; Nanjing Maternity and Child Health Care Hospital: Shuping Han; Qingdao Women and Children's Hospital: Ruobing Shan; The Affiliated Hospital of Qingdao University: Hong Jiang; Children's Hospital of Shanghai: Gang Qiu; Women and Children's Hospital of Guangxi Zhuang Autonomous Region: Qiufen Wei; Children's Hospital of Nanjing Medical University: Rui Cheng; Henan Children's Hospital: Wenqing Kang; The First Affiliated Hospital of Xinjiang Medical University: Mingxia Li; Foshan Women and Children's Hospital: Yiheng Dai; The First Affiliated Hospital of Anhui Medical University: Lili Wang; Shanghai First Maternity and Infant Hospital: Jiangqin Liu; Yuying Children's Hospital Affiliated to Wenzhou Medical University: Zhenlang Lin; Children's Hospital of Chongqing Medical University: Yuan Shi; The First Affiliated Hospital of Zhengzhou University: Xiuyong Cheng; The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China: Jiahua Pan; Shaanxi Provincial People's Hospital: Qin Zhang; Children's Hospital of Soochow University: Xing Feng; Wuxi Maternity and Child Healthcare Hospital: Qin Zhou; People's Hospital of Xinjiang Uygur Autonomous Region: Long Li; The Second Xiangya Hospital of Central South University: Pingyang Chen; Qilu Children's Hospital of Shandong University: Xiaoying Li; Hainan Women and Children's Hospital: Ling Yang; Xiamen Children's Hospital: Deyi Zhuang; Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine: Yongjun Zhang; Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine: Jianhua Sun; Shenzhen Children's Hospital: Jinxing Feng; Children's Hospital Affiliated to Capital Institute of Pediatrics: Li Li; Women and Children's Hospital, School of Medicine, Xiamen university: Xinzhu Lin; General Hospital of Ningxia Medical University: Yinping Qiu; First Affiliated Hospital of Kunming Medical University: Kun Liang; Hebei Provincial Children's Hospital: Li Ma; Jiangxi Provincial Children's Hospital: Liping Chen; Fuzhou Children's Hospital of Fujian Province: Liyan Zhang; First Affiliated Hospital of Xian Jiao Tong University: Hongxia Song; Dehong People's Hospital of Yunnan Province: Zhaoqing Yin; Beijing Children's Hospital, Capital Medical University: Mingyan Hei; Zhuhai Center for Maternal and Child Health Care: Huiwen Huang; Guangdong Women and Children's Hospital: Jie Yang; Dalian Municipal Women and Children's Medical Center: Dong Li; Peking Union Medical College Hospital: Guofang Ding; Obstetrics & Gynecology Hospital of Fudan University: Jimei Wang; Shenzhen Hospital of Hongkong University: Qianshen Zhang; Children's Hospital of Zhejiang University School of Medicine: Xiaolu Ma; Advisor: Joseph Ting; University of Alberta.

Data availability statement

The datasets for this article are not publicly available because part of the data is included in another article under preparation. Requests to access the datasets should be directed to YC, yuncao@fudan.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Children's Hospital of Fudan University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

WX, RB, ZL, and CY: study concept and design. WX, RB, XG, SJ, YW, LL, JS, YC, WZ, SL, ZL, and CY: acquisition, analysis, and interpretation of data. WX, RB, XG, and SJ:

drafting of manuscripts. All authors: critical revision of the manuscripts for important intellectual content. XG and SJ: statistical analysis. SL: obtained the funding. BZ, YD, LL, JS, YC, WZ, ZL, and CY: administrative and technical or maternal support. JS, YC, WZ, and SL: supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.943244/full#supplementary-material

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EDITED BY
Britt Nakstad,
University of Botswana, Botswana

REVIEWED BY
Olugbenga A. Mokuolu,
University of Ilorin, Nigeria

*CORRESPONDENCE
Audrey R. Odom John
johna3@chop.edu

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Prevention of malaria in pregnancy: The threat of sulfadoxine-pyrimethamine resistance

Sesh A. Sundararaman and Audrey R. Odom John*

Department of Pediatrics, Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

Malaria infection in pregnancy can lead to adverse outcomes for both the pregnant person and fetus. The administration of intermittent preventative therapy (IPTp) with sulfadoxine-pyrimethamine (SP) during pregnancy (IPTp-SP) improves outcomes, including severe maternal anemia, placental malaria infection, and low infant birth weight. The WHO recommends IPTp-SP for pregnant individuals living in areas of moderate or high malaria transmission in Africa. The current regimen consists of two or more doses of SP starting as early as possible in the second trimester, at least 1 month apart. Unfortunately, rising *Plasmodium falciparum* SP resistance throughout Africa threatens to erode the benefits of SP. Recent studies have shown a decrease in IPTp-SP efficacy in areas with high SP resistance. Thus, there is an urgent need to identify new drug regimens that can be used for intermittent preventative therapy in pregnancy. In this review, we discuss recent data on *P. falciparum* SP resistance in Africa, the effect of resistance on IPTp-SP, and studies of alternative IPTp regimens. Finally, we present a framework for the ideal pharmacokinetic and pharmacodynamic properties for future IPTp regimens.

KEYWORDS
malaria, drug resistance, low birth weight, antimalarial, IPTp

Introduction

Malaria, caused by parasites of the genus *Plasmodium*, is a major cause of morbidity and mortality across the globe (1). The majority of malaria-related deaths occur in sub-Saharan Africa, and are caused by one parasite species, *Plasmodium falciparum*. Children, especially those under the age of five, are at highest risk of severe disease. Partial immunity, which develops through repeated exposure, provides some protection against both symptomatic and severe disease (2).

While the risks of malaria decrease with age and regular reinfections, they recur again in pregnancy, where both symptomatic and asymptomatic infection have significant consequences for the pregnant person and fetus. This burden is felt disproportionally by pregnant people in sub-Saharan Africa, where over 10 million pregnant individuals are likely exposed to malaria each year (1). Intermittent presumptive therapy for malaria in pregnancy (IPTp) with sulfadoxine pyrimethamine (SP) decreases the adverse effects of malaria in pregnancy, but the benefits of this intervention are threatened by increasing SP resistance throughout sub-Saharan Africa (3). New antimalarial therapies are, therefore, needed to ensure continued protection of pregnant people and fetuses.

Malaria in pregnancy and intermittent preventative therapy

The WHO estimates that over 10 million pregnant individuals (34% of all pregnancies worldwide) are exposed to malaria each year (1). The risks of malaria are increased in pregnancy (4, 5). Not only does pregnancy represent a state of transient immunosuppression, the malaria parasite *Plasmodium falciparum*, expresses a unique adhesion factor, var2csa, that binds chondroitin sulfate on the placenta (6). Parasite adhesion to the maternal surface of the placenta leads to increased inflammation and reduced placental blood flow (6). For these reasons, placental malaria contributes to poor outcomes for both the birthing parent and developing fetus. Malaria during pregnancy contributes to maternal anemia, low birthweight, intrauterine growth restriction, preterm delivery, stillbirth, and death in the neonatal period (7–9). In spite of these many potential complications, pregnant individuals may yet present with few or no symptoms, making prompt identification and treatment of infection difficult (5). Early studies showed that antimalarial prophylaxis in pregnancy reduced maternal anemia and increased infant birthweight (10, 11). This led the WHO to recommend that pregnant people in malaria endemic regions receive intermittent antimalarial prophylaxis.

Currently, intermittent preventative therapy for malaria in pregnancy (IPTp) consists of treatment doses of sulfadoxine pyrimethamine (SP), starting in the second trimester (12). IPTp-SP improves outcomes for both the pregnant person and fetus. Early clinical trials of SP during pregnancy showed a marked reduction in peripheral parasitemia, maternal anemia, placental malaria, preterm birth, and an increase in infant birth weight (13–16). Additional studies showed that three or more doses of SP, given at least four weeks apart, further decreases the overall prevalence of low birth weight and preterm birth (17, 18). The WHO estimates that current levels of IPTp coverage prevent over 400,000 cases of low birthweight each year.

Resistance to sulfadoxine pyrimethamine

The benefits of IPTp-SP in pregnancy are threatened by rising SP resistance in *P. falciparum*. Sulfadoxine and pyrimethamine both inhibit folate synthesis in malaria parasites, acting on dihydropteroate synthase (*dhps*) and dihydrofolate reductase (*dhfr*), respectively. SP resistance develops through the accumulation of mutations in these enzymes (Figure 1). In East Africa, parasites containing a combination of three distinct *dhfr* mutations (N51I, N59R, and S108N) and two *dhps* mutations (A437G, and K540E) have become highly prevalent. The presence of these parasites, termed "quintuple mutants," is highly predictive of treatment failure of clinical malaria in sub-Saharan Africa (19, 20). Acquired immunity likely also plays a role, as treatment failure is observed in young children infected with less resistant parasites (21).

While the presence of quintuple mutants predicts poor treatment response in cases of acute uncomplicated malaria, *P. falciparum* continues to evolve higher levels of resistance. In East Africa, additional mutations, including *dhps* A581G, *dhfr* I164L, and *dhps* A613S/T have begun to emerge. These mutations, when present on the quintuple mutant background, further increase SP resistance and increase the risk of clinical

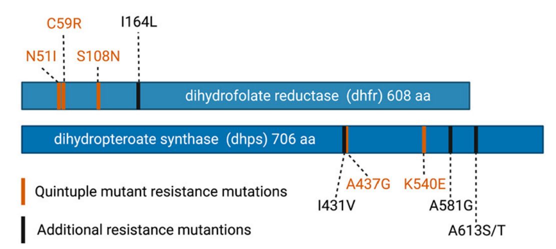

FIGURE 1
Mutations in dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) that confer resistance to sulfadoxine pyrimethamine. Mutations found in the highly resistant "quintuple mutant" are shown in orange. Additional mutations, that are increasing in prevalence in Africa, are shown in black. Figures generated in Biorender.

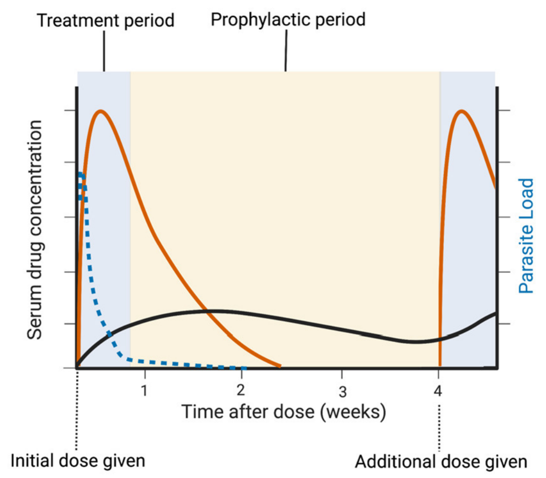

FIGURE 2
Idealized IPTp regimen. A treatment dose of a drug that meets MMV TPP-1 (management, orange line) eradicates existing asexual and placental infection (dotted blue line). A drug that meets TPP-2 (chemoprevention, black line) provides long-term protection against re-infection until the next prenatal visit.

treatment failure (3, 22). A581G and A613S/T mutations have also been detected in West Africa, in the absence of K540E (23). While the lack of K540E in these parasites increases their susceptibility to SP, the risk of highly resistant parasites emerging in West Africa, through the acquisition of K540E or other novel mutations, remains.

The effects of sulfadoxine pyrimethamine resistance on IPTp-SP

Early studies of IPTp-SP in areas of increasing SP resistance showed continued benefit. A 2007 meta-analysis by Kuile, et. al. found that IPTp-SP maintained effectiveness in preventing low birth weight, maternal anemia, maternal parasitemia at delivery, and placental malaria, even in geographic regions where SP treatment failure rates in children with acute malaria ranged from 9–39% (24). Importantly, treatment failure in children appears to occur at lower levels of SP resistance than in adults. Thus, pediatric malaria treatment failure rates are a surprisingly poor proxy for the effectiveness of ITPp-SP in pregnancy (21). More recent studies, using genetic markers of SP resistance, have found that IPTp-SP effectiveness is indeed reduced in areas where highly resistant parasites are prevalent. Van Eijk, et. al. found that the relative risk reduction of IPTp-SP on malaria-associated pregnancy outcomes decreased with increasing prevalence of the K540E mutation (25). While IPTp-SP confers some benefit in areas where the prevalence of K540E was >90%, the benefit was lost in areas where A581G prevalence was >10%. The loss of effectiveness, due to A581G, was also observed by Chico et al. (26). Given the increasing prevalence of A581G in East Africa (23), these data suggest that decreased IPTp-SP effectiveness will soon be widespread in this region.

Dihydroartemisinin-piperaquine as an alternative to IPTp-SP

As the efficacy of IPTp-SP wanes due to increasing resistance, there is an urgent need to identify alternative pharmaceutical strategies for preventing adverse pregnancy outcomes from malaria. While clinical studies have examined multiple alternatives, including amodiaquine, mefloquine, azithromycin, and chloroquine, most have failed due to adverse effects or lack of benefit (27–29). Recently, combination therapy with dihydroartemisinin plus piperaquine (DP) has been proposed as a replacement to IPTp-SP, given the tolerability and rapid, potent activity against asexual *P. falciparum*. IPTp-DP reduces the prevalence of both clinical and sub-patent malaria infection as compared to IPTp-SP (30–32). This has not, however, translated to a consistent improvement in birth outcomes. Thus, far, three randomized controlled trials have found IPTp-DP to be equivalent to IPTp-SP, and only one has found it to be superior in preventing adverse birth outcomes (30–33).

The lack of benefit of IPTp-DP, relative to IPTp-SP, for birth outcomes, in spite of a decrease in detectable peripheral parasitemia, suggests that the latter may not adequately reflect pathology at the placenta (33, 34). Indeed, randomized controlled trials comparing IPTp-SP to intermittent screening and treatment (IST), where pregnant individuals are screened by rapid diagnostic test or peripheral smear and treated only if positive, have found IST to be inferior (33, 35). Moreover, an analysis of over 1,500 patients found that placental malaria infection was associated with lower birth weight regardless of whether parasites were detected in the peripheral blood, and that the presence of peripheral parasitemia, without placental infection, was not associated with lower birth weight (36).

There are multiple possible explanations for the lack of consistent benefit of IPTp-DP over IPTp-SP. First, levels of SP resistance may not have reached thresholds that compromise IPTp-SP. To date, trials comparing IPTp-DP to IPTp-SP have been conducted in areas where the prevalence of A581G and other highly resistance genotypes is low (0–5.8%) (31, 33, 37, 38). In the absence of these highly SP resistant parasites, it is possible that IPTp-SP and IPTp-DP are equally effective in preventing adverse birth outcomes. Second, the frequency of DP dosing may be insufficient to maintain protection. Pharmacokinetic analyses of pregnant individuals given IPTp-DP found that higher exposure to piperaquine was associated with reduced odds of placental malaria, preterm birth, and low birth weight (39). Future studies of IPTp-DP may need to test alternative DP dosing regimens, such as weekly administration, and should be focused in areas of high SP resistance (39).

Future directions

The decreasing effectiveness of SP in East Africa, and lack of a clear alternative IPTp regimen, highlight the importance of continued research into IPTp options. Important areas of focus will include the development of novel therapeutics, establishment of drug resistance markers that correlate with loss of IPTp effectiveness, and discovery of non-invasive methods to detect the presence of placental malaria infection prior to delivery.

Development of novel therapeutics

If DP proves superior to SP for IPTp, its usefulness may unfortunately be short-lived due to evolving resistance patterns in *P. falciparum*. There is evidence for emerging artemisinin resistance in Africa, and piperaquine resistance in South East Asia (40, 41). The rise of both SP and DP resistance highlights the need for continued development of new antimalarials for the treatment of clinical malaria and intermittent preventative treatment in pregnancy. To address this ongoing need, the Medicines for Malaria Venture (MMV) has proposed two Target Product Profiles (TPPs) for antimalarial drug development (42). TPP-1 applies to medications for acute malaria treatment, with essential parameters that include activity against resistant parasites, rapid onset of action, and a large (>12 $\log_{10}$) reduction in asexual parasite load. TPP-2 applies to medications for chemoprotection, with essential parameters that include a long dosing interval (weekly or longer) and efficacy against the pre-erythrocytic liver stages. The clinical benefit of IPTp-SP is likely due to both eradication of any ongoing malaria infection and temporary prophylaxis against new infection (43); both sulfadoxine and pyrimethamine remain detectable in serum for more 40 days after dosing (44). An ideal IPTp regimens should thus aim to meet both TPPs for optimum benefit (Figure 2). However, antigametocyte and antihypnozoite activities, to eradicate the sexual transmission stages or the latent liver stages of *P. vivax* or, respectively, are not necessary for IPTp.

Drug resistance markers to predict IPTp effectiveness

While combined *dhps* K540E and A581G mutations are an important genetic marker of decreasing IPTp-SP effectiveness in East Africa, the generalizability of these markers to other parts of Africa will likely be limited. There is significant variability in the prevalence of *dhfr* and *dhps* resistance mutations across the continent. In West Africa, the A581G mutation is found in the absence of K540E and is associated with increased susceptibility to SP, relative to parasites containing both mutations (3, 25, 45, 46). However, other mutations, such as *dhps* I431V, appear to be emerging. Additional studies are necessary to determine the effects of this I431V on the effectiveness of IPTp-SP. Phenotypic drug resistance studies of field isolates to SP, will also be useful. While traditional *in vitro* assays are limited by the substantial technical challenges of culture-adapting large numbers of field isolates, short-term *ex vivo* drug sensitivity assays can be used to phenotypically screen fresh clinical isolates (47–49). The identification of *ex vivo* phenotypic markers, such as MIC or IC_{50}, that correlate with clinical IPTp-SP failure could allow for generalizability to areas with distinct *dhfr* and *dhps* genetic backgrounds.

Detection of placental malaria infection

Current studies of IPTp are hindered by the inability to assess the presence and degree of placental malaria infection. While the goal of IPTp is to improve outcomes for both the pregnant person and fetus, confounders make it difficult to monitor the clinical effectiveness of IPTp and to compare it across populations or studies. Accurate identification of placental malaria requires labor-intensive histopathology or studies of placental blood, and can only be performed after delivery. Data from studies of IPTp-DP suggest that peripheral parasitemia, even when identified by molecular methods, may overestimate effects on placental infection (33, 36). Future studies would benefit from the identification of new biomarkers of placental infection. These could be derived either from infecting parasites (i.e., levels of var2csa antigen), or the host (i.e., profiles of inflammatory cytokines) (50). Such biomarkers would facilitate longitudinal monitoring of the effectiveness of current IPTp regimens, identification of phenotypic or genotypic resistance markers that predict IPTp treatment failure, and comparisons of new IPTp regimens to current standard of care. They would also help differentiate the benefits conferred by IPTp from other pregnancy interventions, improving our understanding of the effects of IPTp in the evolving field of maternal-fetal health.

Author contributions

AO and SS conceived of this work, and both contributed to drafting and editing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Britt Nakstad,
University of Botswana, Botswana

REVIEWED BY
Lloyd Tooke,
University of Cape Town, South Africa
Endale Tefera,
University of Botswana, Botswana

*CORRESPONDENCE
Stephen J. Swanson
swan0027@umn.edu

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Every breath counts: Lessons learned in developing a training NICU in Northern Tanzania

Stephen J. Swanson[1,2]*, Kendra K. Martinez[1,2], Henna A. Shaikh[3], Godbless M. Philipo[1], Jarian Martinez[1] and Evelyine J. Mushi[1,4]

[1]Department of Paediatrics, Arusha Lutheran Medical Centre, Arusha, Tanzania, [2]Global Pediatrics Program, University of Minnesota, Minneapolis, MN, United States, [3]Global Health Center, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [4]Department of Paediatrics and Child Health, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa

Introduction: Neonatal mortality rates in resource-limited hospitals of Sub-Saharan Africa (SSA) remain disproportionately high and are likely underestimated due to misclassification of extremely preterm births as "stillbirths" or "abortions", incomplete death registries, fear of repercussions from hospital and governmental authorities, unrecorded village deaths, and cultural beliefs surrounding the viability of premature newborns. While neonatology partnerships exist between high income countries and hospitals in SSA, efforts have largely been directed toward improving newborn survival through neonatal resuscitation training and provision of equipment to nascent neonatal intensive care units (NICUs). These measures are incomplete and fail to address the challenges which NICUs routinely face in low-resource settings. We draw on lessons learned in the development of a low-technology referral NICU in Tanzania that achieved an overall 92% survival rate among infants.

Lessons learned: Achieving high survival rates among critically ill and preterm neonates in SSA is possible without use of expensive, advanced-skill technologies like mechanical ventilators. Evidence-based protocols adapted to low-resource hospitals, mentorship of nurses and physicians, changes in hierarchal culture, improved nurse-infant staffing ratios, involvement of mothers, improved procurement of consumables and medications, and bedside diagnostics are necessary steps to achieving high survival rates. Our NICU experience indicates that low-technology solutions of thermoregulation, respiratory support *via* continuous positive airway pressure, feeding protocols and infection control measures can ensure that infants not only survive, but thrive.

Conclusions: Neonatal mortality and survival of preterm newborns can be improved through a long-term commitment to training NICU staff, strengthening basic neonatal care practices, contextually appropriate protocols, and limited technology.

KEYWORDS

neonatal intensive care unit (NICU), physician training, prematurity, kangaroo care (kc), global neonatology, Tanzania, Sub-Saharan Africa, neonatal mortality (NM)

Introduction

Neonatal mortality now comprises approximately half of under-5 mortality worldwide (2.4 million out of 5 million yearly deaths) with the highest burden in Sub-Saharan Africa (SSA). Within the first month of life, prematurity (36%) and birth asphyxia (24%) remain the leading causes of death (1, 2). Moreover, there are an estimated 2 million stillbirths each year and 40% of these are thought to be due to preventable intrapartum events (3). Combining these, neonatal and perinatal deaths surpass 3.2 million each year, with 1.4 million deaths (43%) occurring in SSA (1–3). Not only are stillbirths (including fresh stillbirths) not included in overall mortality data, but many neonatal deaths and stillbirths are neither appropriately recorded nor issued a death certificate—suggesting that current neonatal mortality statistics underestimate the magnitude of the problem (4). In Tanzania, the neonatal mortality ratio (NMR) in 2020 remains high at 20 per 1,000 livebirths (90% uncertainty interval 14–29) (1). Globally, neonatal deaths account for 3% of annual mortality (all ages, both genders), but in Tanzania neonatal deaths comprise 11% of all-age mortality and 33.5% of under-5 mortality (5).

With over 1.3 billion people, Africa remains the second most populous continent with a 3.4% growth rate (6). Wide disparities exist within and between countries in the availability of specialists, sub-specialists, and trained neonatal nurses. A recent survey of 49 African countries indicated that 12 countries had no neonatologists, 21 countries had <50 pediatricians, and specialty neonatal nursing care was recognized in only 57% of surveyed countries (7). Any improvement in global neonatal outcomes requires rapidly increasing the implementation of evidence-based maternal and neonatal care in hospitals throughout low- and middle-income countries (LMICs) (8). Yet, many barriers exist including staffing constraints, cultural beliefs that extremely low birthweight (ELBW, <1,000 g) infants cannot survive, lack of neonatal knowledge and skillsets, poor provision of neonatal respiratory care, lack of appropriate medical equipment and medications, and competing healthcare priorities within health systems (7, 9–11). In this article we will share our journey in the development of an East African neonatal intensive care unit (NICU) and the subsequent effect on neonatal mortality.

A NICU's journey in Northern Tanzania

The early years

In 2013, Arusha Lutheran Medical Center (ALMC) was in its fifth operational year, a 145-bed hospital offering care for ∼10,000 inpatients (children and adults) and 108,000 outpatients annually and with dramatic year-over-year patient growth. Twenty-eight physicians (13 specialists) and 136 nurses were on staff, including two obstetricians and two pediatricians. Like many African hospitals, ALMC relied largely on junior doctors (interns and medical officers) to see most patients and experienced a 10% turnover of staff each year. Furthermore, it's "NICU" consisted of a single, ill-equipped room adjacent to the obstetric ward where unstable newborns were placed—a unit added as an afterthought for babies too ill for the post-partum ward. Oxygen delivery was limited and donated equipment (e.g., radiant warmers, incubators, and phototherapy lights) frequently malfunctioned and lacked replacement parts. Necessary equipment, consumables, and essential medications were largely absent or dependent on inconsistent international donations. Infants in respiratory distress relied on makeshift bubble continuous positive airway pressure (bCPAP) setups utilizing 100% FiO_2.

Compounding this was a significant shortage of Tanzanian nurses and doctors qualified to work in a NICU. Nurses were assigned 6–8 infants and rotated to a different hospital department (medicine, surgery, pediatrics, labor ward, and clinics) every 3 months—a widespread nursing practice still employed in many African hospitals based on a conviction that nurses (and doctors) should be able to care for all patients with equal competence. Because of this, nurses oriented to the NICU routinely failed to achieve necessary procedural skills or familiarity with common newborn conditions. Interns and the medical officer ("registrar") responsible for NICU patients similarly lacked formal training in either pediatrics or neonatology. Few written protocols existed to guide medical decisions with contextual relevance for an African hospital. With these staffing challenges and knowledge gaps, a baby's deterioration in the NICU often went unnoticed until little could be done.

Not surprisingly, our overall NICU mortality rate was 19–24% during 2013–2014 (Table 1). For ELBW infants, the mortality rate was 80% (Table 2) and extremely preterm infants rarely survived. ALMC, however, was not a unique story and faced similar challenges to many hospitals across SSA—where NICU outcomes appear deceptively better due to classification of live births ≤28 weeks gestation as "abortions" or "stillbirths".

Building a NICU starts with nurses

In late 2014, we simultaneously undertook many steps to begin improving the NICU, including expanding the unit and removing non-functional equipment. One of the most foundational steps involved redefining the role of nurses. With support from nursing leadership, mandatory nurse rotations ended, yielding a more stable nursing team. We partnered with experienced volunteer NICU nurses from the USA and Canada to build skills and knowledge among our nurses. Short-term volunteer stints were highly discouraged unless the nurse

TABLE 1 NICU total admissions, prematurity, referrals, surgical admissions, and adjusted survival by year from 2013 to 2021.

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total admits (YoY % Δ)	117 (-)	222 (90%)	236 (6%)	209 (−11%)	251 (20%)	238 (−5%)	316 (33%)	325 (3%)	340 (5%)
Premature (% of total)	49 (42%)	75 (34%)	74 (31%)	104 (50%)	84 (33%)	74 (31%)	129 (41%)	144 (44%)	175 (51%)
Outborn referrals (% of total)	25 (21%)	111 (50%)	119 (50%)	95 (45%)	87 (35%)	60 (25%)	149 (47%)	130 (40%)	169 (50%)
Surgical (% of total)	11 (9%)	18 (8%)	20 (8%)	14 (7%)	9 (4%)	14 (6%)	22 (7%)	28 (9%)	29 (9%)
Gross survival rate	81%	76%	80%	82%	90%	88%	90%	87%	87%
Adjusted survival rate	82%	77%	81%	83%	90%	93%	92%	93%	92%

Adjusted survival (%) excludes admitted newborns with congenital cardiac defects, gastrointestinal or major birth anomalies, or preterm neonates ≤ 25 weeks' gestation, as these newborns are unable to survive in most NICU settings in SSA. YoY, Year-over-Year.

TABLE 2 NICU admission and survival rates by birthweight categories and interventions by year 2013–2021.

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total admits	117	222	236	209	251	238	316	325	340
<1,000 g ELBW admissions (survival rate)	–	10 (20%)	14 (29%)	20 (45%)	14 (64%)	10 (33%)	13 (73%)	22 (79%)	32 (74%)
1,000–1,499 g admissions (survival rate)	–	27 (67%)	16 (56%)	35 (71%)	21 (71%)	24 (74%)	35 (91%)	44 (83%)	59 (85%)
1,500–2,499 g admissions (survival rate)	–	58 (90%)	59 (89%)	47 (96%)	69 (97%)	48 (93%)	82 (97%)	86 (91%)	78 (99%)
Interventions									
bCPAP (% of total)	22 (19%)	69 (31%)	79 (33%)	74 (35%)	81 (32%)	72 (30%)	180 (57%)	207 (64%)	228 (67%)
Pulmonary surfactant (% of total)	N/A	N/A	N/A	N/A	22 (9%)	27 (11%)	47 (15%)	58 (18%)	65 (19%)
Phototherapy (% of total)	40 (34%)	95 (43%)	92 (39%)	110 (53%)	122 (49%)	111 (47%)	164 (52%)	179 (55%)	194 (57%)

(-) data not recorded or incomplete. Pulmonary surfactant widely unavailable in Tanzania prior to 2017. (N/A) Pulmonary surfactant widely was unregistered and widely unavailable in Tanzania prior to 2017.

instructor had previous experience and established relationships with our NICU staff. On average, clinical nurse instructors came for 4 continuous months (range: 6 weeks—2 years), allowing time to learn our hospital system, strengths and limitations, cultural differences and, most importantly, build trust and comradery with Tanzanian nurses. Visiting nurse instructors partnered with Tanzanian nurses in an accompaniment role without removing work duties from local nurses.

Basics of nursing care were prioritized, including thermoregulation, non-invasive respiratory support, neurodevelopmental positioning, feeding and nutrition, infection control measures, and safe delivery of medications. Tanzanian nurses were assigned to care for specific infants to increase accountability and continuity of care. Patient assignments became an accepted new approach, as "everybody's baby is nobody's baby". Use of nursing assessments were encouraged, and intentional efforts were made to involve nurses in daily rounds and clinical decisions. This worked to reduce the preexisting physician-nurse divide and emphasize the value of nursing judgment. Nurses were encouraged to speak to physicians when concerned about the status of a baby or unclear about a medication or plan. In time, the NICU became known as a supportive environment and greater numbers of nurses wanted to work there, and a 1:3 nurse-to-baby staffing ratio was able to be achieved (many large SSA hospitals continue to staff at 1 nurse per 20+ NICU infants).

Accompanying doctors

Another important step was the implementation of physician mentorship to promote deeper knowledge and skills specific to neonatology. According to estimates, there are only 0.23 doctors per 1,000 people living in SSA with an urgent need to educate more doctors (12, 13). Nonetheless, most literature on global health education focuses on learners from high-income countries (HIC)s who spend time in LMICs. In our experience, training doctors is a long-term process of accompaniment. Below, we list key tenets that have served us as we have accompanied doctors in this process.

First, we reduced dysfunctional hierarchies and encouraged team members at all levels to speak up. In Tanzania, the legacy of colonialism mixed with a cultural respect for elders and the need to uphold the ideal of community promotes a strict hierarchy whereby learners, junior doctors, and nurses rarely challenge their superiors. Yet we know patient outcomes improve when medical teams function cohesively and all members are encouraged to speak up (14, 15). This can be modeled in the unit as we navigate diagnostic uncertainty and cognitive biases with humility by readily welcoming challenges as learning opportunities and openly valuing others' opinions.

Second, we created safe learning environments. There must be adequate and supportive supervision so that trainees can make mistakes without harming patients. There is no room for shaming when promoting growth (16, 17). Doctors should never be punished nor humiliated for making unintended mistakes, and they should be celebrated for acknowledging their learning gaps and asking questions. In other words, we granted doctors the "permission not to know" and provided ample educational resources.

Finally, we encouraged critical thinking and attention to detail rather than regurgitating memorized facts. We can help doctors develop skills for synthesizing clinical information into a coherent assessment so they can formulate diagnostic and management plans while accounting for clinical uncertainty and personal cognitive biases (18). We can also emphasize the importance of details, especially when working with newborns, as small changes can make a huge difference. These skills equip learners to continue refining their capacity to manage sick newborns even after we leave.

While short-term education trips and virtual trainings have their utility, the tenets we list above are best taught at the bedside through long-term, in-person accompaniment. Through this model we have seen four former junior physicians (registrars) from ALMC go on to become consultant pediatricians in Tanzania, with more registrars currently pursuing or soon to begin their pediatric residency training.

Partnering with families

Attention was also given to the NICU parents and caregivers who were encouraged to actively participate in daily cares and share their concerns regarding their infant with the medical team. Despite not having sufficient space for an appropriately sized kangaroo care unit, parents routinely employ skin-to-skin (kangaroo care) at every opportunity in the NICU. Families are also taught how to fortify expressed breastmilk using locally available formula and use of a secured feeding tube to feed their preterm infant or infant on bCPAP. As communication between parents and providers increased, we gradually shifted away from the physician-centric model of care.

Judicious use of technology

The use of technology in our NICU was intentionally kept simple. NICUs in LMICs operate in a very different context and serve to meet different needs from those in HICs (19, 20). In HICs, systems for addressing basic newborn care (e.g., newborn resuscitation, infection prevention and control, nutritional support, etc.) are relatively strong, so therapies to improve survival focus on increasingly technologically sophisticated solutions (e.g., conventional and oscillator ventilators, therapeutic cooling, ECMO, etc.). HICs also have many well-trained staff to install and maintain complex equipment. Contrastingly, problems like hypothermia, infection, hyperbilirubinemia, poor nutrition, and respiratory distress among moderately to late preterm infants remain rampant in LMICs (21–23). These problems are better addressed by carefully applying simple concepts and technologies.

Introducing complex technologies into a setting that is not ready to receive them can lead to more harm than good. There are many treatable neonatal conditions that do not rely on complex technologies and should be employed to save newborns in LMICs. In Africa, wide disparities persist between and within countries in the availability of basic, low-technology neonatal respiratory care (i.e., access to nasal prongs, use of high flow heated and humidified oxygen, surfactant, and CPAP). For example, 74% of surveyed African countries reporting that CPAP was available in <10% of cities with a population of more than 150,000 (7). Lifesaving, effective, low-cost technologies remain both inequitably distributed and poorly adopted in many hospitals today.

At ALMC, no ventilators are used in the NICU. Instead, we go back to the basics: thermoregulation, non-invasive respiratory support, optimizing nutrition, and infection prevention/treatment. In 2021, 228 of 340 infants (67%) in the NICU were treated with bCPAP (Table 2) which significantly improves survival rates in LMICs (24). Importantly, we are careful to use warmed, humidified air and oxygen blenders while also performing meticulous nasal care and therapeutic infant positioning. For infants with severe respiratory distress, we pair this with judicious and timely administration of pulmonary surfactant (often administered through a laryngeal mask airway) (25). Additionally, we are elevating our reliance on kangaroo care, which reduces both hypothermia and rates of infection (26). We've also prioritized infection prevention, including intravenous line care and minimizing shared medications and IV fluids. Through investment in a point-of-care EuroLyser Cube[1] assay, which measures quantitative values of C-reactive protein (CRP) from a drop of whole blood, we can trend a non-specific marker of inflammation and better balance the need for early antibiotic treatment for suspected sepsis with antibiotic stewardship (27). Our focus is on early introduction of enteral feeds, rapid feeding advancement with breastmilk fortification, and sodium monitoring/replacement therapy—measures to improve nutrition and achieve optimal weight gain, as nutrition remains the best way to help neonates help themselves. Lastly, we've tackled simple pathologies like hyperbilirubinemia by using a transcutaneous bilirubinometer to detect dangerous levels of hyperbilirubinemia and promptly treat with phototherapy (23). While we've invested in some technologies, our primary focus remains investing in physicians and nurses who can recognize infants' needs and continue to build out a sustainable NICU going forward. Our 92% survival

1 https://www.eurolyser.com/medical-diagnostics/parameter/crp-test/

rates suggests that survival of preterm and critically ill term babies in Tanzania is possible.

Many studies have shown that therapies developed for HICs do not save lives, and may even lead to greater mortality, when used in LMICs. This was demonstrated in the HELIX trial of therapeutic hypothermia for asphyxiated neonates as well as a recent trial which found greater mortality among sick neonates cared for in incubators compared to kangaroo care (26, 28). Newborns in LMICs undeniably deserve the same caliber of care as newborns in HICs; meeting this goal requires first building strong foundational care practices before utilizing more advanced technologies.

Moreover, a recent review found that in SSA, while up to 70% of medical equipment is donated, only 10–30% of this equipment remains operational (29). In the current state, opportunities for failure arise throughout the supply chain of donated medical goods. An inherent power imbalance between donating and receiving parties, along with a lack of collaborative planning often leads to a mismatch between what equipment is needed and what is donated. Once it arrives in the recipient country, equipment designed for HIC can quickly become damaged when exposed to high temperatures and humidity, dust, and fluctuating electricity voltages common in LMIC. Once damaged, equipment is difficult to repair, since trained biomedical engineers and technicians are rare and spare parts often need to be imported—an expensive and time-consuming process (30). Furthermore, NICUs in LMICs often receive equipment from various manufacturers—each with their own upkeep, repair protocols, and spare parts (29). This leads to so-called "equipment graveyards", where equipment lies defunct, simply taking up valuable space (19, 20, 31).

Efforts to ameliorate these challenges are ongoing. There are calls for greater partnership between donating and receiving institutions so that donated goods better meet local needs. Some non-governmental organizations (NGOs) and distributors, including NEST360[2] and Kenya-based HATCH Technologies[3], respectively, are attempting to provide appropriately durable equipment with biomedical engineering support for sustained use. Finally, ongoing efforts to support local innovation can help meet technological needs and foster healthcare system independence (19).

Saving newborn lives in LMICs requires looking beyond technologies used in HICs. Respiratory support of the NICU baby through conventional mechanical ventilation or high frequency oscillatory ventilation does not exist anywhere in northern Tanzania. Our training workshops consistently addresses questions by local healthcare authorities on whether a mechanical ventilator should be a prerequisite piece of equipment for a unit to call itself a "NICU" —reflecting a widespread belief that technology is what separates LMIC from HIC provision of care. Not surprisingly, our own past NICU history and outreaches to other hospitals suggest that neonatal deaths occur among babies due to aggressive and improper use of mechanical ventilation, particularly in settings where nurses and physicians are poorly trained and supportive measures (i.e., proper suction, portable x-rays, and blood gases) are lacking. Reliance on the possibility of mechanical ventilation ("if the baby deteriorates, we can put him on the ventilator") may lead to neglect of a baby who might otherwise survive through prompt use of blended, warmed, and humidified CPAP, timely administration of pulmonary surfactant, and anticipatory nursing care. Use of mechanical ventilation in the NICU further diverts limited nursing care away from CPAP babies to the highest acuity, now-ventilated NICU baby. Multiple nurses may become bystanders, watching the baby on the ventilator at the neglect of other important nursing duties. This was our first-hand experience before we "retired" our ventilator due to space constraints and poorer outcomes. As such, we make every effort to help a baby survive through non-invasive respiratory measures.

2 https://nest360.org

3 https://www.hatch-tech.org

ALMC NICU today

From 2013–2021, our NICU annual census increased from 117 to 340 admissions, representing an annual growth rate of 14% over 8 years (Table 1). Gross survival rates have been 87–90% since 2018, and adjusted survival rates are ≥92% (Table 1). At present, ALMC does not have any mechanical ventilators in the unit, and yet in 2021 we were able to achieve an overall 90% preterm survival rate, with 74% and 85% survival rates for infants weighing <1000 grams and 1000–1499 grams, respectively (Table 2). This stands in contrast to the initial years of 2014-2015 when our survival rates for ELBW infants was 20-29% and 1000–1499 gram infant survival was 56–67% (Table 2). Currently, most of our very low birth weight (VLBW, <1500 grams) infant deaths occurs among transfers from referring private or public hospitals (or home deliveries presenting to the emergency department), where initial post-delivery stabilization is often lacking, and arrival comes too late. In 2021, 51% of all ALMC NICU admissions were preterm neonates and 50% of all admissions were outborn births. High-risk obstetric patients and ELBW/VLBW babies are now routinely referred to our hospital because of the presence of an established NICU. In 2021–22, our smallest survivor was 24 weeks gestation, and smallest recorded birthweight was 612 grams.

Challenges and opportunities

Continued growth has been limited by lack of physical NICU and kangaroo care bed space as well as nursing shortages worsened by problems with nursing retention. Training a nurse to become a specialized NICU nurse is a lengthy process involving many months of supervision, and continued nursing turnover with delays in hiring replacement nurses compromise NICU outcomes and increase nurse: patient ratios. Procurement of needed NICU consumables and essential medications also remains difficult in our local setting, as needed supplies are unavailable through distributors in Tanzania. Some essential NICU drugs (i.e., caffeine citrate) remain unregistered in the country, despite being endorsed in both national Tanzanian and WHO guidelines. Acquisition and importation of needed supplies and equipment for daily operation remains subject bureaucratic obstacles and added clearance fees. Other supplies and medications for NICU babies are increasingly priced above what many families can afford. Striving for long-term sustainability remains hampered by competing hospital priorities, which limits reinvestment of generated revenues back into the NICU. All the while, we continually seek to make improvements sustainable and access equitable. To date, ALMC NICU has never turned away an infant due to payment issues with the belief that every baby deserves a chance live and thrive, regardless of family income and location of birth. Funding for our NICU initiative is often achieved through local fundraising efforts and international small donors when internal revenue falls short.

In 2021, we published our NICU protocol manual, "Every Breath Counts: Manual of Neonatal Care and Drug Doses" written for East African hospitals (32). This manual, along with a paired conference in which 55 hospitals participated (Tiny Feet, Big Steps: Advancing Care of Critically Ill and Premature Babies in Tanzania), created a venue to advance neonatology education and offer resources written in an East African hospital, for an African setting. Our NICU continues to engage local and national government officials through sharing of our neonatal outcomes and protocols, leading workshops in neonatology in both public and private hospitals, and hosting the annual Tiny Feet, Big Steps neonatology conference. Public and private hospital training of nurses and doctors in neonatology has been part of our earliest mission. We have established a national reputation for our training workshops, conferences, written protocols and manual, and the consistent demonstration of what can be achieved in a low-resource, low-technology NICU setting in Tanzania.

Discussion

We remain committed to the ideals that public-private partnerships and NGOs can work to improve neonatal outcomes in LMICs. However, an approach that moves beyond helping babies survive toward helping NICU infants thrive must be adopted. Teaching and equipment must be accompanied with intentional efforts to build a culture where nurses are elevated, anticipatory and proactive approaches rewarded, and an expectation of a future healthy life exists for hospitalized infants. Training both nurses and doctors is a journey of accompaniment where team hierarchy is minimized, and safe learning environments with daily patient assessments are encouraged. Physician and nurse champions of the NICU must mentored and valued by hospital administration. Protocols and NICU guidelines need to be written that are both evidence-based and adapted for contexts where medications and diagnostics may be limited. Widely held beliefs that idealize equipment and promote the need of technology to catapult a LMIC hospital into sudden HIC status must be challenged. There are no shortcuts to developing a NICU that can achieve a survival rate of ≥92%. Our outcomes have reflected consistent investment in training and proper staffing levels of motivated NICU nurses and doctors, building a culture of respectful teamwork, and consistent focus on the basics of care. A NICU in a lower-resource region of Africa need not replicate norms of HICs, but focus on essential skills that promote thermoregulation, prompt respiratory support, optimal nutrition, and infection control. Educating hospital management, government officials and ministries of the importance of essential-yet-unavailable NICU drugs (i.e., caffeine, pulmonary surfactant, NICU IV fluids, vitamin D, and levetiracetam) and everyday consumables (i.e., appropriately sized oxygen cannulas and oro/nasogastric tubes, CPAP supplies, quality IV cannulas, tape and syringes) remains as important as any expensive equipment. In the rush to build and equip NICUs in SSA, the additional building blocks of medications, consumables, needed point-of-care tests, properly trained nurses and physicians, appropriate staffing ratios, and a culture of physician-nurse-caregiver teamwork in the NICU is critically important. This is a journey that cannot be achieved with a hurriedly constructed room, donated equipment, and some training workshops. It is a journey of accompaniment that requires patience, advocacy, and hope. It is a lesson in the importance of transforming medical culture to achieve outcomes once considered impossible, but now a reality.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SS conceptualized, designed the study, and performed the data analysis. SS, GP, JM, and EM contributed to interpretation. KM, SS, and HS drafted the initial version of the manuscript.

GP and EM performed the data collection and were involved in the analysis. JM structured the data and performed the analysis. All authors participated in critical revision of the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Ashish KC,
Uppsala University, Sweden

REVIEWED BY
Intan Silviana Mustikawati,
Universitas Esa Unggul, Indonesia
Abhrajit Ganguly,
University of Oklahoma Health
Sciences Center, United States

*CORRESPONDENCE
Helen Brotherton
helen.brotherton@lshtm.ac.uk;
helen.brotherton@nhs.scot

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Barriers and enablers to kangaroo mother care prior to stability from perspectives of Gambian health workers: A qualitative study

Ying Chun Cho[1], Abdou Gai[2,3], Brahima A. Diallo[2], Ahmadou Lamin Samateh[4], Joy E. Lawn[1], Melisa Martinez-Alvarez[2,5] and Helen Brotherton[1,2]*

[1]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine (LSHTM), London, United Kingdom, [2]MRC Unit the Gambia at LSHTM, Fajara, Gambia, [3]Pediatric Department, Edward Francis Small Teaching Hospital, Banjul, Gambia, [4]Ministry of Health, Gambian Government, Banjul, Gambia, [5]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine (LSHTM), London, United Kingdom

Aims: Kangaroo mother care (KMC) is an evidence-based intervention recommended for stable newborns <2,000 g. Recent trials have investigated survival benefits of earlier initiation of KMC, including prior to stability, with WHO's iKMC trial showing 25% relative risk reduction for mortality of neonates 1–1.8 kg at tertiary Indian and African neonatal units (NNU). However, evidence is lacking about how to safely deliver this intervention to the most vulnerable neonates in resource limited settings (RLS). Our study aimed to understand barriers and enablers for early KMC prior to stability from perspectives of neonatal health care workers (HCW) in a high neonatal mortality RLS.

Methods: This qualitative study was conducted at Edward Francis Small Teaching Hospital (EFSTH), the main neonatal referral unit in The Gambia. It was ancillary study to the eKMC clinical trial. Ten semi-structured interviews were conducted with all neonatal HCW cadres (4 nurses; 1 nurse attendant; 5 doctors; all Gambian). Study participants were purposively selected, and saturation was reached. Thematic analysis was conducted using Atun's conceptual framework for evaluation of new health interventions with methods to ensure data reliability and trustworthiness.

Results: HCW's perceptions of early KMC prior to stability included recognition of potential benefits as well as uncertainty about effectiveness and safety. Barriers included: Unavailability of mothers during early neonatal unit admission; safety concerns with concomitant intravenous fluids and impact on infection prevention control; insufficient beds, space, WASH facilities and staffing; and lack of privacy and respectful care. Enablers included: Education of HCW with knowledge transfer to KMC providers; paternal and community sensitization and peer-to-peer support.

Conclusions: Addressing health systems limitations for delivery of KMC prior to stability is foundational with linkage to comprehensive HCW and KMC provider education about effectiveness, safe delivery and monitoring. Further context specific research into safe and respectful implementation is required from varied settings and should include perceptions of all stakeholders, especially if there is a shift in global policy toward KMC for all small vulnerable newborns.

KEYWORDS

newborn, premature (babies), skin-to-skin care, Kangaroo mother care (KMC), Kangaroo care (KC), Kangaroo method, Health care worker (HCW), qualitative study

Introduction

Complications of preterm birth (<37 weeks' gestation) are the single most common direct cause of death for children under −5 (16%) and for neonates (34%), resulting in 1.1 million neonatal deaths/year (1), with low birthweight (LBW) (<2,500 g) an additional major contributor to neonatal mortality (2, 3). Small, vulnerable newborns are born disproportionately in resource limited settings (RLS) with an estimated 72% of LBW (4) and 81% of preterm neonates (5) born in sub-Saharan Africa (SSA) and Asia. Globally, 30 million neonates require hospital based care every year (6), especially for management of complications of prematurity. Over the last 3 years there has been increasing global recognition and focus on the importance of high quality, facility-based small and sick newborn care (SSNC) in ending preventable neonatal deaths (6, 7). This is urgently required to reach the United Nations Sustainable Development Goal target 3.2 of reducing neonatal mortality to ≤12/1,000 live births by 2030 (8). Despite building momentum and a shift in global policy, critical implementation gaps still exist for SSNC, of which kangaroo mother care (KMC) is central.

KMC was developed in 1978 in South America (9). as a family centered package of care comprising prolonged skin-to-skin contact between newborn and mother or other family member [KMC provider], promotion of exclusive breastfeeding and early facility discharge with close follow-up (10). WHO currently recommends KMC as standard care for stable newborns less than or equal to 2 kg with moderate quality evidence that KMC reduces mortality by 40% compared to conventional incubator care (11). However, nearly half of all neonatal deaths occur during the first 24 h after delivery (12), typically prior to stabilization and in settings lacking neonatal intensive care facilities. Hence, evaluating survival benefits of KMC prior to stabilization was a research priority (11, 13) with several recent or ongoing trials in SSA and India (14–16). The WHO multi-center iKMC trial reported 25% relative reduction in mortality for neonates between 1 kg and 1.8 kg with immediate (median 1.3 h of age) and prolonged (median 16.9 h/day) skin-to-skin contact alongside other SSNC such as bubble continuous positive airway pressure (bCPAP), ventilation and parenteral fluids (15). The iKMC trial findings signal a paradigm shift in SSNC with emphasis on reducing mother-baby separation to promote survival. However, the pragmatic eKMC trial at a more resource limited neonatal unit (NNU) in The Gambia highlighted the challenges of delivering prolonged KMC with substantially lower intervention fidelity (median 6.7 h/d) (14).

Extensive implementation evidence exists for facility-based KMC with stable newborns (17–20) but there is a critical evidence gap for early use with unstable newborns who are a more vulnerable population with specific medical needs. Hence, although there may be overlap, barriers and enablers for KMC prior to stability cannot be assumed to be the same, especially for resource limited settings in which intensive care monitoring and robust health systems may not be available. To date, there is only one small qualitative study from SSA exploring HCW perceptions toward KMC prior to stability, which reported overall acceptability of the intervention to Ugandan HCW (21). There is a paucity of evidence from other RLS with some limited insights into KMC provision on an Iranian maternity unit (22) and feasibility data for ventilated neonates receiving KMC on an Indian NNU (23). HCWs are fundamental for facility-based KMC implementation (20, 24) especially to educate and support KMC providers in delivering KMC. Understanding context-specific HCW perceptions toward provision of KMC to a higher risk, unstable neonatal population is critical for policy and programmatic planning to enable safe and rapid roll-out of this potentially life-saving intervention.

This qualitative study aimed to understand the perceptions of neonatal HCWs toward KMC in unstable neonates <2 kg in a resource limited, high mortality West African hospital setting with exploration of the barriers and enablers influencing early and prolonged KMC delivery.

Abbreviations: bCPAP, Bubble continuous positive airway pressure; EFSTH, Edward Francis Small Teaching Hospital; HCW, Healthcare worker; HIC, High-income country; ICU, Intensive care unit; IV, Intravenous; LBW, Low birthweight; LMIC, Low- and middle-income country; LSHTM, London School of Hygiene and Tropical Medicine; KMC, Kangaroo mother care; MRCG, Medical Research Council The Gambia; NG, Nasogastric; NMR, Neonatal mortality rate; NNU, Neonatal unit; RLS, Resource limited setting; SSNC, Small and sick newborn care; SRQR, Standards for Reporting Qualitative Research; SSA, Sub-Saharan Africa; WASH, Water, sanitation and hygiene; WHO, World Health Organization.

Materials and methods

Study design and context

A qualitative case study design was used to understand lived experiences of HCW, with data collected using a semi-structured interview guide. This study was ancillary to the eKMC trial, a randomized controlled trial investigating the survival and clinical impact of KMC started within 24 h of NNU admission with mild-moderately unstable neonates <2 kg (14).

Study setting

The study was conducted at Edward Francis Small Teaching Hospital (EFSTH) in The Gambia, a low-income country in West Africa, ranked 173 out of 187 on the Human Development Index in 2018 (25). At time of study onset the NMR was 28 deaths/1,000 live births with an estimated 12% of all Gambian newborns born preterm and 17% born LBW (1).

Edward Francis Small Teaching Hospital (EFSTH) was the only teaching hospital and neonatal referral unit in The Gambia. The NNU admits newborns born at the EFSTH maternity ward as well as those born elsewhere, including home deliveries. Approximately 1,400 neonates are admitted annually with case fatality rates 34% for all newborns and 48% for neonates <2 kg (2010–2014). (26) WHO level 2+ care was provided at the time of study onset, with non-servo controlled incubators (5 functioning), radiant heaters (3), cots (24), bubble CPAP (bCPAP) (3), oxygen *via* concentrators (2), 1 functioning pulse oximeter and burettes for IV fluid administration with availability of 1 fluid pump for blood transfusions. Mechanical ventilation, surfactant, umbilical catheterization and parenteral nutrition were not available. KMC for stable newborns was implemented as standard care in 2017, provided on an 8-bed KMC unit adjacent to the NNU and provided to neonates <2 kg with normal cardiorespiratory status and not requiring oxygen or IV fluid therapy for whom a willing KMC provider was available. KMC prior to stability was introduced in May 2018 as part of eKMC trial implementation with two adult-sized beds provided on the NNU for KMC providers (mothers or other relatives) to provide skin-to-skin contact to trial participants (newborns) alongside other necessary treatments. Alterations to patient flow, reconfiguration of areas within the NNU and provision of additional electric points and an oxygen concentrator were also required for provision of KMC prior to stability. One or two trained nurses and one nurse attendant worked per shift with one research nurse per shift also contributing to clinical care, support of KMC providers and performance of all KMC duration monitoring activities. Medical cover was provided by one consultant neonatologist, one medical officer and two house officers per 24 h shift. KMC was provided to mild-moderately unstable neonates during the study period, as per eKMC trial definitions which were based on cardio-respiratory parameters such as heart rate, respiratory rate and oxygen saturation (SpO_2) and whether oxygen was required. Neonates receiving bCPAP or who were hypoxic (SpO2 <88%) and/or needing cardio-pulmonary resuscitation were classed as being severely unstable and did not receive KMC (27).

Study population and sampling

The intended study population was HCW with experience of delivering early KMC prior to stability. This included nursing staff (university trained nurses and nurse attendants) and doctors of varying seniority. Purposive sampling was used to select participants from different roles and seniority levels in order to achieve a range of perspectives representative of neonatal HCW (28). Participants were recruited until thematic saturation was reached (29, 30).

Study procedures

Informed consent and recruitment

Potential participants were approached directly by the lead researcher (YCC) and invited to participate by letter. Written informed consent was then obtained in English language, which all participants were fluent in.

Data collection and management

Data was collected during July-August 2018. Interviews were conducted in English using a semi-structured interview guide (Supplementary material 1) in non-clinical rooms at EFSTH at the participants' convenience when they were not on clinical duty. Interviews were recorded on an Olympus WS-853 digital voice recorder. The interviewer was a trained non-Gambian female clinician (YCC), supervised by an experienced qualitative researcher (MMA). She played no role in clinical care or the eKMC trial, although was also supervised by the eKMC lead investigator (HB). The interview duration ranged from 50 to 89 min (average 61 min). The researchers were cognizant of potential social desirability bias, due to the study being embedded in the eKMC trial and recognized that participants may be reluctant to voice negative perceptions of the intervention. To mitigate this the interviewer (YCC) did not engage in any eKMC trial related activities. Internal validity was maintained by one interviewer conducting interviews. Debriefs with a more senior researcher (HB) were done after the first five interviews and included reflexive observations.

Audio-recordings of the interviews were transferred to a password-protected computer after each interview and transcribed verbatim by the interviewer to ensure consistency and dependability (31). Eight consecutive transcriptions were checked for accuracy by two independent English native speakers. Confidentiality was maintained by use of unique identification codes used in all study logs and transcripts.

Analysis

Data were analyzed using thematic analysis, as outlined by Braun and Clarke (32) using Atun's conceptual framework intended to evaluate the integration of new health interventions (33). This framework has previously been applied in a systematic review of evidence for KMC implementation for stable newborns (34). The framework contains multiple dimensions corresponding to important health system functions: (1) *problem*–health problem targeted by the intervention, (2) *intervention*–including its definition and attributes, (3) *adoption system*–involving multiple key actors and context within which they operate, (4) *health system* and (5) *broader context* (Figure 1). As the problem of small vulnerable newborns has been extensively described elsewhere in the literature this was not included in the analysis.

Transcripts were deductively coded line-by-line by the interviewer (YCC), with concepts labeled in relation to the study aim with a word or a phrase. NVivo 11 (QSR International, Cambridge, MA) was used to assist coding and theme identification. Codes were aggregated into sub-themes based on similarity of their relation to each other. The sub-themes were then deductively grouped and merged into themes by applying the key components of the framework, which thereafter were reviewed and refined to ensure relevance to the study aim. Pseudonymized quotes were selected to reflect the themes and sub-themes. This article was prepared according to Standards for Reporting Qualitative research (SRQR) (Annex II) (35). Ethical approval was granted by the Gambia Government / MRC Joint Ethics Committee, The Gambia (Ref. 1610) and the LSHTM Ethics Committee (Ref. 15357).

Results

We begin by describing the participant characteristics and then proceed to present the identified themes and sub-themes, grouped as per Atun's conceptual framework, and providing a narrative description of main findings as perceived by Gambian HCWs.

Participant characteristics

Ten HCW participated: four trained nurses, one nurse attendant and five doctors (Table 1). All participants were Gambian nationals and underwent undergraduate medical or nursing training at Gambian higher educational institutions, apart from one doctor who was trained in Venezuela and the nursing attendant who received vocational training. Six HCWs had previously been trained on care of the small and sick newborn and KMC (2017) and all had been sensitized about the eKMC trial within the preceding 3-months, including provision of early KMC prior to stability.

Themes and perceptions

Multiple factors were identified as being important for the provision of early KMC prior to stability and are presented as barriers and enablers as per the pre-defined themes from Atun's conceptual framework (Table 2).

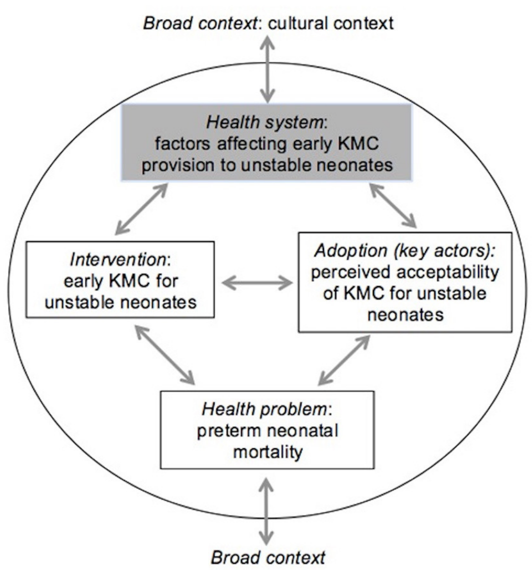

FIGURE 1
Framework for integration of new health interventions, with relevance for KMC prior to stability adapted from (33).

TABLE 1 Demographic and professional details of health care worker participants.

		All	Nurses		Clinicians	
			Registered nurse	Nurse attendant	Medical officer	House officer
	TOTAL	**10**	**4**	**1**	**2**	**3**
Sex	Female	5	3	1	0	1
	Male	5	1	0	2	2
Age (years)	≤30	3	1	0	1	1
	31–40	5	2	0	1	2
	41–50	2	1	1	0	0
Newborn care experience (years)	<1	3	1	0	0	3
	1–3	4	1	0	2	0
	>3	3	2	1	0	0

Intervention (early KMC prior to stability)

All participants were aware of KMC as a method of care for small vulnerable newborns with recognition that skin-to-skin contact is a key component. Participants overwhelmingly expressed positive attitudes toward KMC for stable neonates, regardless of their HCW role, seniority or experience. There was good understanding of the benefits of KMC, which participants identified as: breastfeeding promotion; faster weight gain; early discharge and avoidance of infections. Participants recognized the important role of KMC for thermal control, especially if incubators or radiant warmers were unavailable, as "*caregivers are just like radiant warmers*" as the nursing attendant observed. Participants drew on their professional experience of KMC for stable newborns and cited examples of positive outcomes compared to conventional incubator care, as mentioned by one doctor *"I've seen a lot of improvement with the contact of mother and baby…is even more better than putting babies in incubator"* [HCW01].

In contrast, there were divergent perceptions of early KMC prior to stability with no consensus amongst HCWs about acceptability of the intervention. There was limited understanding about the rationale for providing KMC to unstable neonates and half of the participants were hesitant about the intervention, with three junior HCW expressing more doubts and one doctor commenting that *"I think it's best to wait until at least the first 24 to 48 h before we initiate KMC [to the unstable neonates], because those are just critical, and you want to be on top of things"* [HCW05]. More than half the HCW thought that early KMC could prevent hypothermia and two HCW mentioned enhanced neonatal stabilization as a potential benefit. All cadres of HCW expressed uncertainty about the effectiveness of the intervention, with one nurse preferring not to implement early KMC prior to stability unless recommended by global guidelines: *"For the stable ones, it works pretty well, but for the unstable ones, I can't say that it's working… that well"* [HCW04].

Other participants accepted that KMC could be provided alongside other treatments, with extrapolation of existing knowledge of KMC for stable newborns especially regarding benefits of thermal control: *"The temperature is very important to preterm babies, as they can lose [heat] very easily. The skin-to-skin contact is beneficial as well. So, I believe it's part of the treatment, giving other treatment shouldn't stop you from doing KMC."* [HCW01] Two doctors believed that KMC should be provided for *"as long as the mother can"* [HCW01] although target duration was not mentioned by any HCW. More experienced neonatal HCW expressed more acceptance of the intervention, with an expectation by more senior HCWs that early KMC could be beneficial if proven to be safe.

Adoption system (health care workers and KMC providers)

The adoption system refers to the key actors involved in provision of the intervention and their interests, values and interactions (33). As both HCW and KMC providers (mothers and families) are important actors in this complex intervention (36), this theme was sub-divided to enable consideration of factors related to each actor.

Factors related to health care workers

Perceptions of KMC prior to stability relating to HCW factors centered on three sub-themes: (1) Importance of HCW education; (2) Safety of KMC alongside other small and sick newborn care interventions; (3) Need for vigilant clinical monitoring of unstable newborns receiving skin-to-skin contact.

TABLE 2 Barriers and enablers for delivery of KMC prior to stability, as perceived by Gambian health care workers.

	Intervention: KMC prior to stability	Adoption system: Acceptability of early KMC prior to stability to key stakeholders		Interaction with health system	Cultural context
		Health care workers	KMC providers		
Barriers	• Limited understanding of rationale • Uncertainty about effectiveness	• Safety concerns -IV fluid administration -IV cannula dislodgement -KMC wrappers -Infection risk -Gastric tube feeding • Lack of clinical monitoring	• Availability of KMC provider -Illness, post-operative, admitted at another facility -Domestic responsibilities -Prolonged admission • Physical discomfort -Tiredness, back pain -Sleep disturbances -High ambient temperature • Lack of privacy/respectful care • Negative perceptions of KMC • Lack of understanding -Communication barriers	• Health system limitations -Lack of adult beds -Lack of space with risk of overcrowding -Limited WASH and cooking facilities • Staffing shortages	• Exclusion of fathers from newborn care • Socio-cultural norm of carrying newborns on back • KMC as new practice in The Gambia
Enablers	• Transfer of knowledge from existing KMC practices • Recognition that early KMC may improve thermal control and stability	• HCW education and experience -HCW prior experience -Continuous education including at antenatal clinics • Methods for safe IV fluid, oxygen and gastric tube feeding • Pulse oximetry monitoring during KMC prior to stability • Task shifting to reduce HCW workload	• Family support -Provide KMC -Emotional support • Education of KMC providers -Benefits and safety of KMC -Compliance with HCWs • Empowerment as main carer -Enhanced bonding -Effects of KMC on newborn • Peer-to-peer support	• Comfortable environment -Distractions (e.g., TV) -Cooking and WASH facilities • Reduced HCW workload • Rationalization of scarce resources • Improved patient flow with earlier discharge	• Prominent role of women during perinatal period • Buy-in from fathers • Community sensitization

HCW, health care worker; IV, Intravenous; KMC, Kangaroo mother care; NNU, neonatal unit; TV, Television; WASH, Water, Sanitation and Hygiene..

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Importance of HCW education

Education of HCW about the importance and practicalities of early KMC prior to stability was seen as central for successful delivery, for both permanent HCW and rotating junior doctors and nurses. Expanding education activities to include HCW in antenatal clinics was also suggested by two senior nurses to enable prenatal sensitization and facilitation of KMC as soon as possible after delivery: *"If you tell them that since at the antenatal clinic, they will be aware of it..., they will be preparing for it, so it would not be a problem"* [HCW11].

Concerns about safety of KMC alongside other small and sick newborn care

Safety of the intervention was an important sub-theme with concerns expressed by all participants, but especially more junior HCW. One nurse expressed concerns that newborns could deteriorate if KMC is started too early. Participants also voiced concerns about providing early KMC in specific high risk clinical scenarios, such as: apnea; respiratory distress; severe jaundice requiring phototherapy; blood transfusion; convulsions or high fever.

Views on the provision of early KMC alongside other SSNC interventions varied according to the type of treatment. KMC given simultaneously with IV fluids was considered feasible but 6 participants, mostly junior HCW, expressed concerns regarding safe IV fluid provision with use of the KMC wrapper. Specific concerns included occlusion of IV lines if KMC wrappers were tied tightly or incorrectly and risk of peripheral venous cannula dislodgement due to flexed position or compression of limbs within the KMC wrapper. One doctor noted that *"They tie [the wrappers] on top of the fluid, so it compressed the vein and even IV fluids, the giving set, it compressed so it stopped"* [HCW02]. Two doctors described experiences in which neonatal dehydration or hypoglycaemia had occurred during KMC provision to unstable neonates, which they attributed to the intervention. Half of the participants reported that IV cannulas had become dislodged during provision of the intervention and raised the possibility that seclusion in the KMC wrapper would delay detection of cannula problems.

Practical solutions to promote safe IV fluid delivery whilst in KMC position were suggested. These included secure placement of cannulas in upper limbs (not lower limbs), positioning of hands outside of the KMC wrapper, education of KMC providers about appropriate wrapper tying and limitation of movements and observing fluid drip rates in-order to promptly identify fluid administration problems.

Several HCW also reported a perceived increased risk of infection associated with the effect of KMC on IV cannula sites, with one doctor observing that *"sometimes skin-to-skin contact, you see mother is sweating and when they sweat, sometimes they get, the cannula got sweat. And those are risk factors of polluting, infections to the line"* [HCW01].

Oxygen provision was not thought to be affected by KMC delivery unless the newborn was severely unwell, but some participants did identify this as a concern for KMC providers. An experienced doctor commented that *"The mothers sometimes are a bit worried, they think it [oxygen] is going on and off when they move up and down, but we explain to them that we secure it correctly and they can receive it fully "* [HCW08]. A senior nurse identified the importance of securing the oxygen prongs with tape.

Perceptions of the use of nasogastric (NG) tube feeding whilst in KMC position varied, with participants expressing contradictory views about whether KMC aided feeding or exacerbated the risk of milk aspiration from being compressed within the KMC wrapper. Junior HCWs expressed more reluctance regarding NG feeding alongside KMC with one junior doctor stating *"Because they [are] compressed, and the child might regurgitate or vomit when they're being fed in that position"* [HCW05].

Need for vigilant clinical monitoring of unstable newborns during KMC

The need for vigilant clinical monitoring of unstable neonates was highlighted by several participants with a general reluctance to place unstable neonates in KMC position without direct observation and continuous pulse oximetry monitoring. Specific concerns included that the KMC wrapper may prevent visual observation of unwell neonates and timely detection of illness, with one doctor commenting that *"You have a critical child who needs a lot of supervision, who needs to be looked at, you need to visibly see these children"* [HCW05].

Four experienced HCWs perceived that KMC providers play an important role in monitoring unstable newborns, with one doctor stating that *"the mom is in contact with the baby 24 h, as soon as something happens, it [she] would notify. So, it's actually better than not doing it early"* [HCW06].

This task shifting of the supervisory role onto KMC providers was valued by several HCW as a way of reducing HCW workload as HCWs were just there to *"monitor and supervise"* [HCW8], as said by one senior doctor. Only one nurse reported increased workload due to attending to KMC providers' needs.

KMC providers

Several factors relating to KMC providers were viewed as being important for delivery of early KMC prior to stability, including: (1) Availability of the mother during the early admission period with family support; (2) Physical discomfort, especially during sleep; (3) Importance of privacy during skin-to-skin contact; (4) Education of KMC providers in context of high compliance with HCW authority; and (5) KMC provider empowerment and peer-to-peer support. Each of these factors are considered in turn below:

Availability of mother with family support

Maternal unavailability on the NNU was the biggest challenge to delivering early KMC, as perceived by all participants. This was attributed to a variety of reasons including: postpartum illness; admission at another health facility or recovery from cesarean section. One doctor commented that *"When the mother is in post*-cesarean-*section, you're not able to transport the mother from postnatal [ward] to this place [NNU], or especially when the mothers, the babies are far, from other health facilities, you might not get the mother in the first 24 h*" [HCW02].

HCW generally viewed KMC prior to stability as an intervention which had to fit around the KMC providers' other responsibilities, with several reasons identified as limiting the delivery of prolonged KMC. These included domestic responsibilities such as childcare of other children, and lack of access to WASH facilities such as toilets, showers and running water. A senior nurse identified that lack of WASH facilities prevented prolonged continuous early KMC, stating that *"Inside there [is] one toilet, so sometimes we go up to 40 something babies, it's difficult, so some they [KMC providers] would not like to use the toilet, they would go down and find where to take bath*" [HCW09]. Prolonged admission was viewed by half of participants as a hindrance to KMC provider's commitment to KMC due to financial burden on the family to provide food and other necessities. Five participants considered that the quality and quantity of hospital provided food did not meet the mother's needs and reported that many mothers rely on families' donations, with an experienced doctor stating that if the length of stay is too long the KMC provider's families can become "*fed up [with] bringing food*" [HCW08].

Family support from grandmothers or aunties was viewed as essential with one doctor sharing that *"sometimes we bring second help as a way of accompanying them to feel that they're at home...not necessarily doing KMC, but to be with them"* [HCW08]. Female relatives were seen by most HCW as feasible alternative KMC providers if the mother was unavailable, with one nurse reporting that *"We once had a mother, the mother was not feeling very well, so a helper was inside helping her. But some of them, their relatives are not here, they came alone here, that is the problem*" [HCW11]. Relatives were also reported to provide emotional support to mothers. However, two nurses expressed a preference for mothers as KMC providers with one nurse commenting that *"We should know which types of helpers we're taking, if the hygiene is poor or you know that this one is not that active, I think we wait for the mother"* [HCW09]. Frequently changing KMC providers and having many additional KMC providers on the NNU was also seen as an infection prevention control risk.

Physical discomfort especially during sleep

Physical discomfort was viewed as the most frequent complaint made by KMC providers. Causes of discomfort were thought to include tiredness and back pain from extended periods carrying newborns in KMC position as well as post-operative pain. The effect of high ambient temperatures was also mentioned as a cause of women's discomfort during KMC.

Sleep deprivation, poor sleep quality and KMC provider concerns about safety of their newborn during sleep were also important barriers for KMC provision, as noted by the nursing attendant: *"They [Mothers] might tell you 'I'm tired, I need to turn, I cannot turn with my child, it's not safe', unless you take the child from them, place them on the radiant heater, allow them to sleep"* [HCW10].

Lack of privacy during skin-to-skin contact

A lack of privacy on the busy NNU was perceived by two female nurses as a key factor limiting the acceptability of KMC to mothers and female relatives, with women reluctant to expose their bodies during skin-to-skin contact, as one nurse observed: *"They [Mothers] said 'No, no, no, I cannot undress myself here inside this public place. They rather, just [let the baby] stay inside the incubators*" [HCW09]. The lack of curtains or screens was identified by one doctor as a possible factor in fathers' infrequent visits to the neonatal and KMC units: *"If one of the fathers has to come to the KMC ward... because the mothers have to be exposed for the skin-to-skin [contact], so [they] could get very awkward and really uncomfortable. It's a shared ward*" [HCW05.] Gowns were provided for KMC providers, but HCW considered that the hot climate precluded women from using them in addition to the KMC wrapper.

KMC provider education in context of high compliance with HCW authority

KMC providers' negative perceptions about KMC prior to stability and lack of understanding were highlighted as important barriers for maternal and family buy-in to the intervention. The capacity of mothers to understand was seen as foundational, with two HCW's commenting that multiple ethnic languages posed a communication challenge and one nurse described some mothers as being *"difficult"* and requiring repeated explanations.

Experienced HCW of all cadres recognized the importance of educating KMC providers about the benefits of KMC prior to stability and how to safely deliver the intervention, with the nurse attendant suggesting that *"There should be everyday, or every 2 days, giving health talk to the mothers for them to know what's the neonatal KMC, because we said in our own languages, so they will understand it more*" [HCW10]. Three participants stated that mothers and other family members would accept intravenous (IV) fluids with KMC if they understood that both treatments were beneficial, as all they [KMC providers] want is "*to see their babies getting well*".

There was general recognition that parents want the best for their newborns and frequent statements about mothers being compliant with HCW's instructions. Many of the participants considered their own role in educating mothers and relatives, with a frequently expressed view from both nurses and clinicians that HCWs garner a high level of respect and can exert a positive influence on parental behavior, as described by one doctor *"Even though initially they feel a bit strange, but it depends on the way you explain to them. So, if you, as a health worker, you show the mother something strange, the mother will take it as strange thing. When you explain to mother that it's normal and it's for the benefit of the child. So, they will do it"* [HCW01]. The importance of the HCW hierarchy was also considered to be a factor in maternal and family acceptance of KMC prior to stability. One clinician perceived that KMC provider compliance may be enhanced if KMC is described as a medical treatment versus a nursing method, although this finding was not reported by nursing HCW.

Empowerment of KMC providers and peer-to-peer support

Mothers' who directly observed beneficial effects of KMC on their newborns' sleep and clinical status were thought to be more accepting of the intervention. One nurse attendant described her experience being told by a mother that *"my child is now used to this KMC"* [HCW10] because the baby was able to sleep more and cried less whilst in KMC position. Enhanced bonding and attachment between KMC provider and newborn was thought to enable KMC for some women. Three participants perceived that spending more time with their newborn as primary care-giver empowered mothers and was an important enabler for delivery of this intervention, as stated by one doctor: '*'They [Mothers] take ownership of the work, they think they're doing the work for themselves… the mothers are very happy with that"* [HCW08].

Peer-to-peer support was also seen as valuable to encourage mothers' uptake of KMC prior to stability with discussion of their experiences in supporting stable newborns and transfer of knowledge for KMC prior to stability. The role of other KMC providers was described by four participants as explaining or translating HCW instructions as well as reminding about feeding times, maintaining hygiene and sharing knowledge about comfortable and safe KMC provision. One senior doctor shared that *"…always one mother who is experienced than the rest, and she takes the lead and takes the charge and teach them"* [HCW06].

Interaction with health system

Participants highlighted several health system limitations affecting delivery of early KMC prior to stability, including provision of a comfortable environment, availability of beds and space, access to cooking or WASH facilities and HCW availability.

Several HCW viewed the environment as important, including access to cooking facilities and, as suggested by one nurse, distractions such as a television to reduce the tedium of staying in hospital for prolonged periods. A senior doctor stated that *"If there's an environment that makes them to feel like home… they have a place where they can cook, they get what they want to cook… will be a great encouragement for mothers to stay as long as they could for the interest of their babies"* [HCW01].

Limited availability of beds for KMC providers on the NNU was also viewed as a key barrier to delivery of early KMC prior to stability by half of the participants, with recognition that beds were required for KMC providers' comfort. A senior nurse stated that *"Because early KMC you need beds, and we don't have space for beds… right now it's only two beds, so if we want to all that unstable babies to start KMC, we cannot"* [HCW09]. Participants also considered the capacity of the NNU space to accommodate additional beds and KMC providers, with concerns about over-crowding leading to higher infection risk. Two nurses were in favor of allowing only mothers onto the NNU due to space limitations and to prevent infection. Establishment of a special ward for provision of early KMC was proposed with views expressed that newborns receiving KMC should be cohorted in a separate area to outborn or potentially infectious neonates in an effort to reduce infection risk for the vulnerable small newborns. The nurse attendant suggested *"[Open up] a special ward with the special nurse,… because different babies are here, not from only the labor ward [in this hospital] but referred from [other] facilities,…so infection might come very easy"* [HCW10].

Limited access to basic water, sanitation and hygiene (WASH) facilities, such as toilets, showers and running water for hand hygiene was seen as interrupting prolonged KMC for both stable and unstable newborns by all participants. Staffing limitations were also thought to influence the clinical monitoring and management of unstable neonates receiving KMC with the nursing attendant reporting that "*The fluids get stopped overnight, when most staff, we have few staff on the ground and sometimes the mothers also feel sleepy, they cannot observe that the fluid is not flowing at all, so when you come in the morning, this child is already hypoglycemic*" [HCW10]. Three doctors also raised the risks during the night shift when HCW staffing levels are low and KMC providers are sleeping.

Participants identified several benefits for the health system, including reduced HCW workload due to enhanced monitoring by KMC providers, rationalization of scarce resources as *"you just need the mother and child, and that's it"*[HCW05] and improved patient flow through the neonatal unit via enhanced stabilization leading to earlier discharge.

Cultural context for early KMC prior to stability

The importance of gender roles within newborn care decision making was highlighted by all HCWs, with identification of the peripartum period as being dominated by women. Exclusion of fathers from pregnancy, childbirth and child-care was mentioned by four HCWs, with one junior doctor stating that "*it is believed that the whole period, the whole* *puerperium, the childbirth, the pregnancy is for women, it is not for men, and men are totally excluded from it"* [HCW05]. However, three male participants believed that the father held the ultimate authority within the household and that paternal buy-in and encouragement were necessary for women to engage with the intervention. A senior male nurse commented that *"The mother might not like something, but with the interference of the husband... she will tend to do it [KMC]"* [HCW04].

Community understanding and acceptance of KMC was also viewed by four HCW as being essential so that mothers would not *"feel strange"* for front-carrying their newborns instead of back-carrying, which is the accepted socio-cultural norm. One senior nurse commented that *"Some of them (mothers) think that it's not the safer method, because of the taboo. So, some of them think that the baby should be always at the back, not in the front, that's our belief here"* [HCW04]. Community sensitization about KMC as a way of caring for small babies and, especially, prior to stability, was suggested as a strategy to enhance individual buy-in, with recognition that KMC is a relatively new practice in The Gambia.

Discussion

This qualitative study presents novel insights for delivery of KMC prior to stability on a West African resource limited NNU with value for regional roll out if global policy change occurs. Important barriers included: Maternal unavailability early in NNU admission; Physical discomfort of the KMC provider; Perceptions around unsafe delivery alongside other small and sick newborn care interventions; and health system infrastructure and resource limitations including lack of space, beds, WASH facilities and staffing. Key enablers included: HCW training with consideration of "task-shifting" onto KMC providers; Provision of respectful care for KMC providers; Sensitization of mothers, fathers, families, communities; and peer-to-peer support.

Unavailability of mothers during early NNU admission was a foundational barrier with multiple reasons identified why mothers were not available at our study site. Over one-fifth of newborns in the eKMC trial intervention group were born by Cesarean section, with 52% of the trial cohort born at another health facility (14) and geographical separation of the EFSTH neonatal and maternity units. Understanding the precise reasons for maternal unavailability is important to help facilitate earlier maternal presence and will likely vary between health facilities. Involving other family members as alternative KMC providers may mitigate early maternal unavailability, as identified by HCW in this study and as per the eKMC trial in which 46% of the intervention arm received first KMC from a female relative (14). Female relatives are willing to support mothers in this role (36) and are influential newborn care decision makers in many African communities (37, 38). Hence, involving female relatives, especially elders, in policy and programs may assist with delivery of this complex intervention.

Physical discomfort experienced by KMC providers, especially during sleep, was seen as a key barrier for prolonged KMC prior to stability. Sleeping supine or upright whilst in KMC position is a recognized barrier to KMC practice in both LMIC (20, 34) and HIC settings (39) and resources such as pillows, washable mattresses and secure, comfortable KMC wrappers can relieve KMC provider discomfort (20, 34). Mothers are recovering from child birth at time of early KMC initiation, therefore issues pertaining to mothers' physical health and sleep quality likely play a greater role in delivery of early KMC compared to KMC later in the postnatal period. An effective strategy during the iKMC trial was the establishment of "mother-neonatal ICUs", with joint maternal and neonatal management in a shared space with input from specialist neonatal and maternity HCWs (15). Further insights into implementation of "mother-neonatal ICU's" from the iKMC trial is awaited, especially costing tools and data to inform infection prevention control planning, which was a specific concern expressed by our participants with regards to overcrowding and presence of multiple family members on busy NNUs.

Safety was a key concern for our participants, especially regarding safe IV fluid administration whilst in KMC position. This contrasts with Ugandan HCW, who had no safety concerns themselves but reported that Ugandan mothers were concerned about IV tubing dislodgement during KMC (21). The KMC wrapper was thought to impact on safe IV fluid provision by Gambian HCW. There is limited data comparing safety of different KMC wrapper types for unstable populations in RLS (40) and this is essential to know prior to widescale implementation of KMC prior to stability. We addressed safety concerns in real-time by refining eKMC trial procedures to minimize disruption to IV fluid administration with enhanced education of HCW at the trial site using recommendations from our findings (Figure 2). Providing KMC to unstable newborns alongside oxygen was not perceived as a barrier by Gambian HCW, consistent with findings from elsewhere in Africa (21).

Clinical monitoring during KMC prior to stability was deemed essential by our participants with pulse oximetry especially important at night due to limited staffing and KMC providers' need to sleep. Both Ugandan HCW and mothers also identified the need for pulse oximetry for unstable newborns receiving KMC (21). However, perceptions varied about the effect of KMC position on monitoring, with recognition that whilst KMC can enable earlier detection of problems such as apnoea by KMC providers, there is reduced direct monitoring by HCW due to encasement within the wrapper (21). There is no evidence that providing KMC to unstable newborns in RLS is unsafe (14, 15, 23), but HCW perceptions or doubts about safety may contribute toward HCW reluctance to comply with any future recommendations to expand KMC to an

- **Position of intravenous (IV) peripheral venous cannula:**
  - Site peripheral venous cannula in dorsum of hand
  - Place hand with cannula in-situ on KMC provider's chest, outside the KMC wrapper
- **Position of IV fluid bag:**
  - Hang IV fluid bag directly behind KMC provider's back, to avoid kinks in tubing
  - Ensure IV tubing is on top of KMC wrapper and not obstructed
- **Advice for KMC providers:**
  - How to secure KMC wrapper safely, without occlusion of IV tubing
  - Avoid sudden movements or frequent changes in position
  - Observe flow rate of IV fluids to identify fast or slow fluid administration
  - Inform health worker if there are any issues with IV fluids or peripheral venous cannula

FIGURE 2
Recommendations to enhance safety of intravenous fluid administration whilst in KMC position.

unstable population. This is an important barrier to HCW buy-in and could be mitigated by involvement of HCW in local implementation and focus on safe IV fluid administration.

Lack of adult beds on the NNU and limited space were key health systems barriers for early KMC prior to stability, consistent with existing implementation evidence for KMC from the perspective of KMC providers (21, 34, 41), health workers and health systems (20, 24). We addressed these findings during the eKMC trial by reconfiguring the NNU to allow space for four adult beds with provision of additional electric points and an oxygen concentrator. This required support from hospital administrators as well as additional funds, highlighting the importance of KMC champions at all health system levels (18) especially strong local leadership and adequate financing (20). Understanding the perspectives of administrators toward health systems change to facilitate KMC prior to stability is essential and a current research gap, along with economic evaluations. Provision of adequate WASH facilities close to the NNU is also an important health system requirement for prolonged early KMC, as identified by Gambian HCWs. This would reduce time that KMC providers spend away from their newborns and also promote infection prevention control practices which our participants highlighted as a specific concern.

Limited staffing levels and high workload can preclude KMC provision for both stable (20) and unstable newborns, as we identified. The iKMC trial provided HCWs with responsibility only for supporting KMC providers, which possibly contributed toward the higher intervention duration delivered (median 16.9 h/d) (15). This contrasts with only 6.7 h/d of KMC delivered in our more pragmatic eKMC trial, when research and hospital personnel had multiple clinical responsibilities and a high workload burden with nursing to patient ratios being as low as 1:40 newborns during peak admission periods (14). Feasible strategies are required to overcome this so that HCW can adequately support KMC providers. Task-shifting of appropriate duties to KMC providers with promotion of family integrated care (42) may mitigate this barrier and our findings suggest that this would be acceptable to Gambian HCW.

HCW training about KMC theory and practice, linked to accessible protocols with supportive programmatic supervision is the cornerstone of existing KMC practice (20, 24) and our findings support this strategy for KMC prior to stability. Sharing knowledge within professional and hospital networks with mentorship visits, peer-led workshops (20) and the Communities of Practice model (43) would also aid implementation. Our participants focused mainly on skin-to-skin aspects of KMC with relatively scant mention of exclusive breastfeeding or feeding support. This absence of HCW focus on feeding was also observed by a systematic review synthesizing existing evidence for barriers and enablers of facility-based KMC in SSA (20). This underlines the importance of comprehensive HCW training including emphasis on promotion of exclusive breastfeeding so as to promote knowledge transfer to KMC providers.

Respectful treatment of KMC providers was seen as an important enabler by Gambian HCW, with privacy perceived as fundamental. This is consistent with an Iranian study in which 83% of midwives considered privacy as a key enabler for KMC in the delivery suite (22) and the OMWaNA feasibility study in which both Ugandan mothers and HCW stressed the importance of privacy on busy NNUs (21). Privacy screens can promote KMC acceptance and delivery in HIC settings (44, 45) and should also be promoted in LMIC settings. Providing a comfortable and safe environment for KMC is consistent with WHO standards for respectful maternal and newborn care (46) which also includes respectful communication between HCW and KMC provider (20).

This study adds to the literature by presenting HCW's lived experiences of delivering early KMC to unstable neonates in an African RLS and provides important contextual insights from a pragmatic research setting with value for future research, practice and implementation. We identified contrasting perceptions of HCW toward KMC prior to stability with doubts expressed about intervention effectiveness. However, interpretation of this is limited, as data was collected during the early phase of the eKMC trial, prior to publication of iKMC trial results and, hence, the effectiveness of the intervention was not known at time of study onset. Our methods were robust with utilization of a relevant conceptual framework (33) and we made efforts to ensure data reliability and trustworthiness such as quality checking of transcriptions and maintenance of internal validity.

Limitations included data collection by a non-Gambian, with potential for misinterpretation of culturally specific findings. Interviews were conducted in English which may not have been the participant's preferred language, despite high fluency levels, and nuanced descriptions may have been missed. Despite efforts to reduce social desirability bias, association with the eKMC trial and the locally well-regarded research institution (MRCG at LSHTM) may have biased our findings. However, as participants expressed mixed perceptions of the intervention with multiple concerns and no overwhelmingly positive HCW perceptions, social desirability bias is unlikely to have played a prominent role. The small sample size is acknowledged but as all HCW cadres were included and thematic saturation was reached, we are satisfied that our findings represent those of Gambian neonatal HCW with experience of supporting KMC prior to stability. Extrapolation to other settings should be done with caution due to the specific factors relating to setting, population and research context. We present a HCW centered perspective and findings related to KMC providers' experiences should be interpreted with caution, as we did not specifically explore the interaction of HCW and KMC providers nor include KMC providers' own perceptions.

Understanding views of other key stakeholders involved in KMC is urgently needed prior to wide scale roll out or policy change. This should include mothers and fathers, the extended family especially female relatives, community women's groups and religious leaders. Understanding the attitudes and priorities of hospital administrators, policy makers and program managers is also critical with economic evaluations at health system, family and societal levels and from varying RLS settings vital for health service planning. Implementation insights from other trials are awaited and will add to this evidence base, with anticipated high value from the OMWaNA trial economic evaluation (16).

Conclusion

Early KMC prior to stability is a life-saving intervention for vulnerable newborns and signals a paradigm shift in family centered small and sick newborn care. Gambian HCW expressed contrasting views toward this intervention with uncertainty about effectiveness and safety concerns especially regarding concomitant IV fluid administration and impact on infection prevention control. Health systems limitations (beds, space, WASH, staffing), unavailability of mothers during the early neonatal period and need for respectful care were deemed as important factors restricting delivery to unstable newborns on this resource limited NNU. HCW training leading to KMC provider education, family and peer-to-peer support and sensitization of fathers and communities were identified as potential enablers. Further context-specific implementation research from varied RLS and all stakeholders is urgently required for health service planning of safe and respectful operationalization of early KMC prior to stability, if this potentially life-saving intervention is recommended by global policy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon request to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by LSHTM Observational Ethics Committee, LSHTM and the Gambia Government / MRC Joint Ethics Committee, The Gambia. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YCC, HB and JEL conceptualized the study. YCC developed the study guides and obtained regulatory approvals with input from MM-A and HB. YCC collected and analyzed the data with support from HB and MM-A. YCC prepared the first draft of the manuscript with substantial input from HB and technical advice from MM-A and BD. All authors contributed towards and approved the final version.

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This work was originally presented as a MsC research thesis (YCC) (47).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.966904/full#supplementary-material

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EDITED BY
Jakub Zieg,
University Hospital in Motol, Czechia

REVIEWED BY
Rupesh Raina,
Akron Children's Hospital,
United States
Katherine Twombley,
Medical University of South Carolina,
United States

*CORRESPONDENCE
Mignon I. McCulloch
mignon.mcculloch@uct.ac.za

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Perspectives: Neonatal acute kidney injury (AKI) in low and middle income countries (LMIC)

Mignon I. McCulloch [1]*, Victoria M. Adabayeri [2], Selasie Goka [3], Tholang S. Khumalo [4], Nilesh Lala [5], Shannon Leahy [5], Nokukhanya Ngubane-Mwandla [5], Peter J. Nourse [1], Beatrice I. Nyann [6], Karen L. Petersen [5] and Cecil S. Levy [4]

[1]Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa, [2]Korle Bu Teaching Hospital, Accra, Ghana, [3]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, United States, [4]Nelson Mandela Children's Hospital, University of the Witwatersrand, Johannesburg, South Africa, [5]Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa, [6]Department of Paediatrics, University of Ghana Medical Centre, Accra, Ghana

Neonatal AKI (NAKI) remains a challenge in low- and middle-income countries (LMICs). In this perspective, we address issues of diagnosis and risk factors particular to less well-resourced regions. The conservative management pre-kidney replacement therapy (pre-KRT) is prioritized and challenges of KRT are described with improvised dialysis techniques also included. Special emphasis is placed on ethical and palliation principles.

KEYWORDS

neonatal acute kidney injury, LMIC, neonatal KRT, neonatal peritoneal dialysis, conservative kidney management

Introduction

Pediatric acute kidney injury (AKI) management is challenging in low- and middle-income countries (LMICs) where facilities for diagnosis and treatment including dialysis are limited. In view of this, prevention and early identification are important, specifically for neonatal acute kidney injury (NAKI) which is common in neonates and especially those admitted to neonatal intensive care units (NICUs). The kidney replacement therapy (KRT) in neonates has been associated with mortality rates of 17–24% as well as longer NICU or hospital stays (1). Newer generation KRT machines for neonates (*CARPEDIEM*® and NIDUS®) have been developed but are not easily accessible in many LMICs and thus there is a need in these regions for appropriate data on KRT in neonates and particularly accessible techniques such as peritoneal dialysis (PD).

Diagnosis of neonatal acute kidney injury

Recognition of AKI (definition and diagnosis) has evolved to the KDIGO AKI definition as per **Table 1** (2).

The neonatal definition should be used for children <120 days and the KDIGO pediatric definition (which is the same as the adult one) thereafter (3). Urine output (UO) is important for the assessment of neonatal AKI (4). However, AKI in the neonates is often non-oliguric (5), and the measurement of UO in neonates is limited by the availability of catheter sizes and the risk of catheter-associated urinary tract infections (UTIs) with sepsis (4).

Limitations

Serum creatinine (SCr) is affected by age, sex, and muscle mass; changing in response to drugs, liver dysfunction, or fluid overload, and requires a baseline value for AKI diagnosis (6). In the neonatal period, maternal creatinine and maturational differences influence the SCr (3). Furthermore, preterm infants often have an initial rise in serum creatinine during the first few days of life before peaking and progressively declining (5). In term infants, serum creatinine gradually declines to reach a nadir by 2 weeks of age and even longer in preterm infants (3, 5). This could inherently be viewed as AKI, however, does not meet the current definition (2). In addition, there are significant delays in creatinine rise following an insult (48–72 h), and >50% function has to be lost before SCr will increase (3). In general, neonates have a low-glomerular filtration rate (GFR) at birth (even lower in premature infants) which gradually improves over the first few months of life, to reach adult values by the age of 2 years (3).

The application of newer biomarkers is a challenge in LMIC. A single-elevated SCr or oliguria should flag AKI to avoid delay in urgent treatment measures (6).

Low- and middle-income countries also experience delayed or unavailability of laboratory results in addition to lack of access to early markers of AKI; alternatively, attention to daily weights and meticulous recording of the absence of wet nappies may alert the clinician to AKI. Scoring systems such as the Renal Angina Index (RAI) become helpful in the early recognition of patients at risk for the development of AKI (2).

More recently, the "Neonatal AKI Risk Prediction Scoring" was devised as the ""STARZ (Sethi, Tibrewal, Agrawal, Raina, waZir)" Score analyzing the risk factors for AKI in neonates admitted to the NICU. This tool includes 10 variables (nine clinical and one laboratory) with a total score ranging from 0 to 100 and a cut-off score of 31.5, and has been successfully validated in a large multicenter cohort (7).

Risk assessment and etiology

Risk assessment of NAKI focuses on perinatal and postnatal risk factor surveillance, and subsequently instituting primary prevention strategies (2), **Table 2** below combines risk factors and common causes of NAKI (2, 8). In LMIC countries, dehydration and primary kidney disease are the commonest causes of NAKI but etiological data is lacking (2).

In addition, nephrogenesis is incomplete in premature neonates thus immature glomeruli, impaired urinary concentrating ability, and autoregulation in neonates are additional NAKI risk factors. Unfortunately, the rates of premature deliveries are higher in LMIC with lower infant survival rates compared to high-income countries (9).

The 0by25 campaign, an International Society of Nephrology (ISN) awareness movement, states that no one should die of untreated AKI in low-resourced countries by 2025 by improving awareness, understanding, and policy implementation (10). Public health measures to provide clean water, endemic infections, environmental exposures, delayed recognition of AKI, accessibility to laboratory services, iatrogenic

TABLE 1 Kidney disease: improving global outcomes (KDIGO) acute kidney injury (AKI) classification including neonatal modifications.

	Pediatric		Neonatal	
Stage	**Serum creatinine**	**Urine output**	**Serum creatinine**	**Urine output**[a]
1	1.5 to 1.9 times baseline OR ≥ 0.3 mg/dl increase*	<0.5 ml/kg/h for 6–12 h	≥ 0.3 rise within 48 h or ≥ 1.5–1.9 × rise from baseline (previous lowest value) within 7 days	≤ 1 ml/kg/h for 24 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥ 12 h	2.0–2.9 times baseline	≤ 0.5 ml/kg/h for 24 h
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥ 24 h OR Anuria for ≥ 12 h	≥ 3 × rise from baseline or serum creatinine ≥ 2.5 mg/dl or renal replacement therapy initiation	≤ 0.3 ml/kg/h for 24 h

[a]Urine output criteria utilized in the AWAKEN study. May also consider utilizing the pediatric urine output data for neonates if the granularity of data allows.
*Increase in SCr by X0.3 mg/dl within 48 h; or an Increase in SCr to X1.5 times baseline, which is known or presumed to have occurred within the prior 7 days. mg/dl, milligrams per deciliter; eGFR, estimated glomerular filtration rate; ml/min, milliliters per min; ml/k/h, milliliters per kilogram (2).

TABLE 2 Causes of neonatal AKI.

Combined risk factors	Prematurity
	Low birth weight
	Maternal risk factors predisposing to premature birth (pre-eclampsia, smoking and alcohol consumption)
	Maternal NSAID exposure
Pre-renal/ Functional AKI	Reduced renal perfusion
	Evaporative losses (premature neonates)
	Blood loss
	Gastrointestinal losses
	Reduced effective circulation/hypoxia
	Reduction in cardiac output
	Birth asphyxia
	Respiratory distress syndromes
	Critical congenital heart disease
	Cardiac surgery/ECMO
	Congenital heart block
	Sepsis syndromes
	Third spacing
	Nephrotoxic agents (therapeutic, traditional medications)
Intrinsic AKI	Tubular interstitial disease
	Ischaemic injury-hypoperfusion
	Asphyxia
	Sepsis syndromes
	Nephrotoxic agents (NSAIDS, Antibiotics)
	Renal vasculature disease
	Thrombosis (venous/arterial)
	Umbilical lines
	Glomerular, cystic disease
	Congenital nephrotic syndrome
	Renal cystic disease
	CAKUT (renal agenesis, dysplasia)
	Infections
	CKD
Post-renal AKI	Obstruction
	CAKUT (PUV, bilateral obstructive uropathy)
	Neurogenic bladder

factors, and response to diagnosis are areas emphasized (10). The campaign describes the "5R's," namely; risk assessment, recognition, response, renal support, and rehabilitation (10).

Preventing further injury

Prevention of neonatal AKI is important in LMIC where resources are limited. Nephrotoxic-AKI is common in hospitalized infants, particularly, infants with VLBW (2, 11). Surveillance, stewardship, and avoidance if possible, of nephrotoxic agents are important. It is known that the burden of neonatal sepsis is high in LMIC with potentially more exposure to nephrotoxic agents such as aminoglycosides being commonly used as first-line agents, however, this data is also lacking [Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) study] (12).

Appropriate monitoring of serum drug levels of nephrotoxic drugs should be instituted (11) but this monitoring is frequently not available in less well-resourced countries in view of the cost of the drug level testing.

Urinary tract infections should be treated promptly to avoid the possibility of further kidney injury.

Secondary prevention strategies include early detection of neonatal AKI with standardized definitions and the use of biomarkers (2), as previously discussed. Tertiary prevention focuses on regular surveillance of long-term AKI complications, such as growth monitoring, blood pressure screening, and imaging to assess scarring of kidney parenchyma to ensure early investigation of possible evolving CKD.

Management pre-kidney replacement therapy

The management of neonatal AKI begins with a thorough history and physical examination to determine risk factors, etiology, and severity of AKI (3). Volume status (hypo-, eu-, or hypervolemic) should be assessed by weight, vital signs, and mental and cardiorespiratory status. In addition, volume intake should be compared to output (urine, stool, and other losses). Urine output should be determined (oli-, non-oliguric, or polyuric) and electrolytes and renal bladder ultrasound obtained. Management of the neonate with AKI continues with achieving and maintaining euvolemia and safe electrolyte status and avoiding further kidney injury.

Volume status

For hypovolemic patients, the fluid deficit should be repleted initially with bolus fluids and subsequent urine output reviewed. Updated Surviving Sepsis guidelines 2020 suggest smaller boluses of fluids at a time with volumes of 10–20 ml/kg/dose, especially in regions where intensive care facilities may not exist (13). Neonates who respond to initial fluid resuscitation can receive continuous fluids to support their maintenance needs and any additional losses. Patients who remain oliguric/anuric, should be fluid restricted to the minimum amount of volume (intravenous plus enteral) needed to prevent hypoglycemia. Hypervolemic patients will need volume restriction dependent on their state of oliguria.

Diuretics augment fluid removal in hypervolemic patients if the cardiovascular status is adversely affected. Frusemide increases urine output but does not alter the natural cause of AKI (3) however it is easier to manage an infant who passes urine than an anuric patient. For neonates, a trial of frusemide 1–2 mg/kg/dose may be given to induce diuresis together with theophylline (14, 15). If this is successful, a frusemide infusion of 0.2–1 mg/kg/h is useful in settings where KRT is not available. Neonates with polyuric AKI (such as infants with posterior urethral valves) are at risk of electrolyte losses and may require replacement.

Electrolyte management

In general, oliguric patients with AKI should have restricted potassium intake (16). Specific therapy for hyperkalemia includes beta-adrenergic agonists *via* nebulizers or intravenous route, loop diuretics, intravenous calcium gluconate (10%), sodium bicarbonate, and cautious use of insulin and glucose therapy [monitoring for hypoglycemia to which neonates are particularly prone is important as even recent adult studies have cautioned against the use of insulin (17)] to shift extracellular potassium into the cells. Enteral cation exchange resins to remove potassium from the body have been implicated in colonic perforation and should be used to decant feeds instead and used only in extreme conditions (18).

Hypocalcemia should only be treated with calcium gluconate in severe cases or if the neonate is symptomatic. Phosphorus restriction, by giving breast milk or low-phosphorus formula, may be required in neonates with hyperphosphatemia, keeping in mind that neonates have a higher phosphate level at baseline. Oral phosphate binders may also be used.

Hyponatremia is often dilutional and free water intake restriction eventually corrects sodium levels in those situations. However, provision of sodium for partial slow correction is warranted in neonates with severe hyponatremia, those with neurological signs, and those with renal losses, with close monitoring.

Metabolic acidosis should be managed with Ringer's Lactate when able, reserving sodium bicarbonate administration for severe cases (16).

Acute kidney replacement therapy—peritoneal dialysis

The concept of "PD first" is the mainstay in many LMICs and also in neonatal AKI as venous access and machines relevant to neonates have historically been unavailable. PD catheters in form of Tenckhoff style catheters placed by surgeons or Seldinger placed catheters placed at the bedside have been successfully implemented (18). Simultaneous airway management and sterile techniques are essential with the creation of artificial ascites to prevent bowel damage prior to catheter insertion.

In situations where formal PD catheters are not available, Cook pigtail catheters, rigid stick catheters (Romsoms) and also improvised equipment such as central lines, chest drains, and nasogastric catheters can be used successfully as taught by the Saving Young Lives (SYLs) initiative.

More research is needed on the recommended prescription and catheters for low-birth weight babies and those used to date are summarized in this review by Burgmaier et al. (19). Prophylactic antibiotics by intravenous administration on insertion of a catheter or intraperitoneal technique prevent peritonitis and heparin can be used in the fluid bags.

Fluid volumes for neonatal AKI are 10–20 ml/kg/cycle with cycles consisting of fill (10–15 min), dwell (30–90 min), and drain (20–30 min) periods. In these small infants measuring devices such as buretrols for fluid administered are essential.

Fluid strengths vary from 1.5, 2.5, or 4.25% dextrose (or similar) and can be used as bicarbonate or lactate based. Locally prepared using buffered intravenous solutions such as Ringers Lactate with 50% dextrose added to form glucose solutions (see PDI guidelines) (17) mixed in a sterile manner have also been used successfully with low-infection rates.

Continuous flow PD (CFPD) using two PD catheters has been shown to significantly increase clearance and ultrafiltration during PD and research looking at gravity-assisted techniques show promise compared with attempting to do this with adapted automated machines (20).

Training teams of doctors and nurses together in improvisation techniques for KRT is part of the SYL strategy.

Acute kidney replacement therapy–continuous kidney replacement therapy

Continuous kidney replacement therapy (CKRT) is increasingly used in neonates with oliguric AKI and associated volume overload or electrolyte derangements, or metabolic emergencies such as hyperammonemia. It is especially useful in neonates who are on ECMO, those who need very quick and high clearance rates (e.g., hyperammonemia) not achievable with PD and neonates with abdominal abnormalities that would not allow placement of a PD catheter or successful use of the peritoneal membrane and hemodynamically unstable patients (21). While CKRT has advantages, one needs to consider that vascular access is needed and carries risks such as infection, the circuit typically needs anticoagulation, the patient may be frequently exposed to blood if a blood prime is needed and, depending on the filter used, may develop bradykinin release syndrome (21, 22). Blood priming is less of an issue if the Cardio–Renal Pediatric Dialysis Emergency Machine (*CARPEDIEM*®), the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS®) or the Aquadex® machines are used (21, 22). While CKRT is currently unlikely to be a frequent option for patients in LMICs given the resources (technical, staffing, and cost) needed, we will review considerations further later.

Continuous kidney replacement therapy achieves fluid removal and clearance through diffusion (CVVHD), convection (CVVH), a combination of diffusion and convection (CVVHDF), and some adsorption (21). For the majority of neonates who are placed on CKRT, either of the options aforementioned is adequate to address the indications for acute dialysis. Double lumen vascular access, even as small as 5 Fr [Arrow® 5Fr 5 cm double lumen 18 and 20 g], 6 Fr

[Powerhohn®], or 6.5 Fr [Gamcath®], is typically needed unless the *CARPEDIEM®* /NIDUS® is being used. Catheter sizes can be as low as 4 Fr, however, if the patient's size would support a larger catheter size, this is preferable to allow for better flow rates and less clotting (21, 22).

For neonates in whom the extracorporeal volume is greater than 10% of their blood volume, a blood prime is recommended (22). Blood flow rates (Qb) should range from 3 to 5 ml/kg/min and the total dialysis dose around 20–25 ml/kg/h (2,000 ml/h/1.73 m^2) keeping in mind that this dose may result in larger clearances for smaller neonates than they would for larger neonates. For anticoagulation, heparin or citrate (not licensed currently in neonates) are most commonly used. Most CKRT dialyzer membranes are replaced every 72 h but newer neonatal machines (e.g., *CARPEDIEM®*) would need 24 hourly changes which are expensive in LMIC settings. Close monitoring of electrolytes is extremely important as is volume status.

Affordability and improvisation when no equipment available

Where kidney replacement therapy (KRT) is indicated for neonatal AKI, very few families in LMICs are able to access centers equipped to perform this therapy (23).

Consequently, AKI is a death sentence for many children in these situations [Challenges of pediatric acute kidney injury in low-income and middle-income countries. Mignon McCulloch, Prasad Devarajan, on behalf of the International Pediatric Nephrology Association (IPNA guidelines)].

Many of these countries have large rural populations living large distances from medical centers. Transport infrastructure is also usually poor which compounds the problem. Consequently, children with AKI often have a delayed presentation with potentially avoidable complications (24).

Due to the unaffordable cost or unavailability of dialysis equipment, various improvisations have been used to perform PD. These include chest drains, nasogastric tubes, urinary catheters, and adult central venous lines, as a substitute for PD catheters as well as bedside prepared dialysis fluids adapted from intravenous fluids (25).

In many centers, only adult extracorporeal dialysis circuits are available and when used in small children may lead to fatal complications. In small babies, it is far better to use peritoneal dialysis than inappropriately sized hemodialysis equipment.

Drug and laboratory tests are mostly self-funded and thus are beyond the reach of the families. Clinicians are often required to make decisions based on experience and best guesses of prognosis without the aid of laboratory tests. Drug availability is also limited with the result that certain medications, especially, antibiotics are not selected according to guidelines, but choices are modified according to funds available.

Chronic kidney replacement therapy

In the chronic KRT (cKRT), there is a need for frequent reviews at a tertiary facility. The need for transportation fares, and accommodation away from home pose a big challenge. Cost of drugs and laboratory tests are even more exorbitant than AKI management and often multidisciplinary teams, namely, dietitians, especially needed in neonatal CKD are non-existent (23).

In the case of chronic PD, storage space for PD fluids, running water, and dedicated sleeping space to perform PD are also limiting factors. The long-term goal for these children should be prepared for transplantation.

Ethical issues around the provision of chronic kidney replacement therapy for neonates in low- and middle-income countries

The decision of whether to embark on a course of chronic kidney replacement therapy (cKRT) for a state-funded neonate in an LMIC requires careful consideration. Improvements in technology and outcomes (26–28) have led to an increase in the number of neonates started on cKRT (29), and the pediatric nephrologist in an LMIC may feel an obligation to commence cKRT for the neonate who needs dialysis. However, good outcomes in this population have only consistently been achieved by skilled teams working in resource-rich environments (30), and neonatal cKRT is not yet universally accepted as appropriate (31).

The discussion should quantify the expected quality of life and prognosis of the child, and address the expected quality of life for the family (32, 33). The physical, psychological, and social burden on the caregivers of children on cKRT is well-documented and the family social situation, distance, and means of transport from the dialysis center and reliability of electricity supply must all be considered (34).

The team should perform an honest appraisal of their ability to provide the requisite medical care (32), namely, the availability of equipment and medication, financial resources, level of medical and surgical expertise, and chances of future transplantation (24). Neonatal and infant dialysis requires lower fill volumes, shorter dwell times, and more frequent exchanges than older children (35). Most automated cyclers have a minimum fill volume of greater than 100 ml, and so the exchanges will initially have to be performed *via* a manual "buretrol" system (29). The neonate started on cKRT can expect to spend many months in an intensive care unit (ICU) setting until they are big enough to be managed on either an automated cycler or on a more manageable manual PD prescription.

Autonomy, beneficence, and non-maleficence all apply to issues in the neonatal ICU (36), but when it comes to commencing cKRT for the neonate in LMICs, the principle of distributive justice will dominate the others due to the critical shortage of neonatal and pediatric ICU beds in these areas (37, 38).

ICU decision-making guidelines in LMICs emphasize the provision of equitable access and optimization of the overall benefit from the ICU resources, and so preference is usually given to children who have conditions with good outcomes, and who are predicted to have relatively short ICU stays (39).

What is unique about providing cKRT to a neonate is the long ICU stay that will be needed, especially, when morbidity can be significant, and long-term outcomes, including the prospect of transplantation, may well be guarded in this setting (30, 40). Perhaps commencing cKRT on neonates is not really a feasible option for most LMICs right now.

Palliative care of the neonate with acute kidney injury

Palliative care provides multidisciplinary, holistic care to improve the quality of life in those with life-threatening or life-limiting illnesses, from diagnosis to bereavement (41, 42) including family counseling and symptom management (41). It is a goal for universal healthcare and should be provided by a specialized palliative team at all levels of care, including at home (41, 42). Palliative care is practiced worldwide, with a lag in pediatrics, especially in LMIC (43). It is not a part of the undergraduate curriculums, and overall knowledge of the goals of palliative care remains low, especially in junior staff (43).

Breaking significant news about a change in the course of illness, or management plan requires delivery in a manner considerate of the setting, people present, and actual information allowing questions and using mutual decision-making ensuring that the family's anticipatory grief is not complicated by excess feelings of guilt or anger (44).

Advanced care planning is performed in a life-limiting illness, to redirect care toward comfort through symptom management, spiritual and psychosocial support. A reduction in invasive monitoring, imaging, and blood tests may be mutually agreed upon, even before the withdrawal of life-supporting therapies (45). Postnatal wards, intensive care units and also neonatal units can be utilized for end-of-life care.

Signs of discomfort should be identified and both non-pharmacological methods (swaddling and sucking) and analgesia provided according to availability and access (45, 46). Symptoms of uremia and electrolyte disturbances such as nausea, agitation, upper gastro-intestinal hemorrhage, and seizures should be managed appropriately, e.g., buccal midazolam for seizures, agitation, and distress.

Oliguric patients may develop symptoms of cardiac failure which may need reduction of intake as well as fentanyl for control of dyspnoea (45, 46). The use of dark bedding can assist in catastrophic bleeding.

Allowing the family an opportunity for memory making including photographs or cultural rituals has been shown to assist parents and siblings with their grief (45).

If possible to assist in planning, an estimated time as well as the place of death (tertiary referral center, a district hospital closer to home, a hospice, or at home) should be made in consultation with the family and entire team ensuring that it is in the best interest of the neonate and family, explaining the changes that may occur at and after death (44, 45). Neonatal units should be encouraged to develop protocols for end-of-life care that include control of symptoms, counseling structures as well as available community resources to support the families of those with AKI.

Future goals

Education around neonatal AKI is an essential part of pediatric training together with advocacy for the development and funding of equipment suitable for these infants. Nephrology organizations, namely, IPNA, ISN, ISPD, and EuroPD with the Saving Young Lives program teaching adaptations and improvisation for PD, and also training fellowships, have come a long way in developing these services. However, advocacy at the hospital and government level in LMIC for funding of equipments is required to keep a focus on neonates with AKI.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MM led the collaboration and planning of the manuscript, writing section and then combining all the sections, proofread, and did final edits and references. VA, SG, TK, NL, SL, NN-M, PN, BN, KP, and CL provided equally in writing separate sections with individual references and then also performed a final proofreading. It was an equal collaboration between a team of paeds nephrologists in LMIC. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Transcutaneous bilirubin-based screening reduces the need for blood exchange transfusion in Myanmar newborns: A single-center, retrospective study

Hiromi Suzuki[1]*, Saneyuki Yasuda[2], Yinmon Htun[3], Nant San San Aye[4], Hnin Oo[4], Thet Paing Oo[5], Zaw Lin Htut[4], Kosuke Koyano[3], Shinji Nakamura[3] and Takashi Kusaka[3]*

[1]Department of Hygiene, Faculty of Medicine, Kagawa University, Kagawa, Japan, [2]Post Graduate Clinical Education Center, Kagawa University Hospital, Kagawa, Japan, [3]Department of Pediatrics, Faculty of Medicine, Kagawa University, Kagawa, Japan, [4]Neonatal Intensive Care Unit, Central Women's Hospital, Yangon, Myanmar, [5]Poole Hospital, University Hospitals Dorset NHS Foundation Trust, Poole, United Kingdom

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EDITED BY
Britt Nakstad,
University of Botswana, Botswana

REVIEWED BY
Tina Marye Slusher,
University of Minnesota Twin Cities, United States
Dag Bratlid,
University of Oslo, Norway
Kristin Braekke,
Oslo University Hospital, Norway

*CORRESPONDENCE
Takashi Kusaka
kusaka.takashi@kagawa-u.ac.jp
Hiromi Suzuki
suzuki.hiromi@kagawa-u.ac.jp

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Background: Neonatal hyperbilirubinemia is a significant health problem in Myanmar. We introduced transcutaneous bilirubin (TcB) measurements in 2017 and developed an hour-specific TcB nomogram for early detection and treatment of hyperbilirubinemia in Myanmar neonates. This study aimed to evaluate whether our screening method for hyperbilirubinemia decreased the requirement of blood exchange therapy (ET).

Methods: This retrospective cohort study was conducted at the Central Women's Hospital, Yangon. Two groups were included as follows: group 1 (control group; comprising infants born in 2016 and screened on the basis of Kramer's rule), and group 2 (intervention group; comprising infants born in 2019 and screened by TcB measurement using a nomogram). The number of ETs was analyzed based on causes of hyperbilirubinemia and number of days after birth.

Results: Groups 1 and 2 comprised 12,968 and 10,090 infants, respectively. Forty-six and two infants in Groups 1 and 2, respectively, required an ET. The odds ratio for ET was 18.0 (Group 1 to Group 2; 95% confidence interval [CI]: 4.8–67.1; p = 0.000). Serum bilirubin values at the time ET was administered were significantly higher in Group 1 than those in Group 2 (median: 23.0 and 16.8, respectively).

Conclusion: The management of hyperbilirubinemia using our screening method (TcB Nomogram) can effectively reduce the need for ET in neonates in Myanmar.

KEYWORDS

blood exchange therapy, neonatal jaundice, infants, transcutaneous bilirubin, phototherapy, nomogram

Introduction

Neonatal hyperbilirubinemia presents a significant health burden in developing countries, such as Myanmar (1, 2). It must be detected and treated early to prevent irreversible bilirubin encephalopathy, permanent neurological deficits, or death of the neonates (3). Phototherapy is an effective non-invasive treatment for neonatal hyperbilirubinemia; early detection of hyperbilirubinemia enables the administration of phototherapy at hospitals, even in developing countries. However, late detection may lead to extreme hyperbilirubinemia, which requires invasive treatments [such as blood exchange transfusion (ET)] to prevent bilirubin encephalopathy and death (4). A previous intervention study conducted in Myanmar revealed that intensive phototherapy could significantly reduce ET rates (5). Therefore, early detection and timely treatment with phototherapy are important to avoid tragic outcomes (6).

In Myanmar, the majority of newborns are delivered at home and may not receive adequate medical care at birth, including home visits and physical examinations by doctors. Some parents do not seek hospital checkups unless the infant shows obvious anomalies or neurological abnormalities. Home birth and self-referral to a hospital are significant risk factors for the presentation of acute bilirubin encephalopathy (7). On the other hand, infants born at hospitals are likely to undergo regular medical observation and examination for hyperbilirubinemia based on Kramer's rule (8), which is highly subjective.

Kramer's rule identifies hyperbilirubinemia based on the dermal change of color on the head, hands, and feet (8). The Kramer score is indicated as follows: (1) jaundice of head and neck; (2) trunk to the umbilicus; (3) groin, including the upper thighs; (4) knees and elbows to ankle and wrists; (5) feet and hands, including palm and soles (8). We are required to score jaundice under natural light by blanching the skin. This method depends on the doctors' judgment based on their knowledge and experience, and on whether the total serum bilirubin level has been checked. Once the total serum bilirubin level is confirmed objectively, newborns are treated with phototherapy or ET according to the American Academy of Pediatrics (AAP) guidelines (6). However, a recent study in Indonesia evaluated the Kramer score as an invalid method for identifying infants in need of treatment (9).

In 2017, we introduced transcutaneous bilirubin (TcB) measurement in a hospital in Yangon based on previous reports of its usefulness in developing countries in terms of feasibility (10–12). As previously reported, TcB nomograms vary among different ethnicities (13). Without considering ethnic differences, we might misjudge the appropriate timing of treating hyperbilirubinemia. For instance, TcB measurements tend to be overestimated in Myanmar newborns with a dark skin tone and underestimated in those with a light skin tone (14). If these Myanmar newborns are assessed using a nomogram that is intended for a different ethnicity with a lighter skin tone, their TcB values will most likely be above the treatment line; thus, they will be over-treated. Therefore, it is necessary to develop a nomogram specific for each target population. Indeed, with the approval of the Ethics and Review Committee of Myanmar, we successfully developed an hour-specific TcB nomogram to achieve early detection for Myanmar newborns in 2017 (15).

Pediatricians and postgraduate students working at a neonatal unit at the hospital were offered training sessions on the use of TcB measurements and the nomogram developed by us. They have started to include hyperbilirubinemia screening with TcB measurement in routine work at the postnatal wards since 2018. Moreover, because this screening method is feasible, it has been widely used by medical professionals. In this study, we evaluated the effectiveness of this new screening method in reducing the number of ET cases.

Materials and methods

This single-center, retrospective cohort study included neonates born at the Central Women's Hospital Yangon, Myanmar after 35 weeks of gestation with a birthweight > 2,000 g. These infants were divided into the following two groups (**Figure 1**): Group 1 (control group; infants born between January and December 2016 who were screened by Kramer's rule), and Group 2 (intervention group; infants born between January and December 2019 who were screened by TcB measurement using our

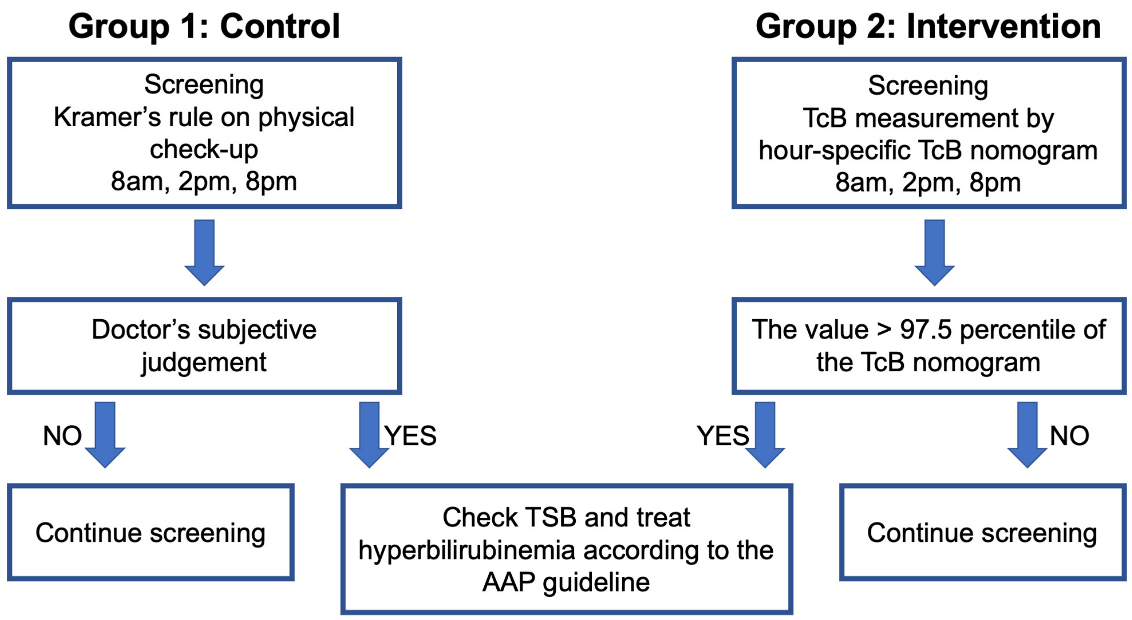

FIGURE 1
Algorithm of the control and intervention groups for the treatment of hyperbilirubinemia.

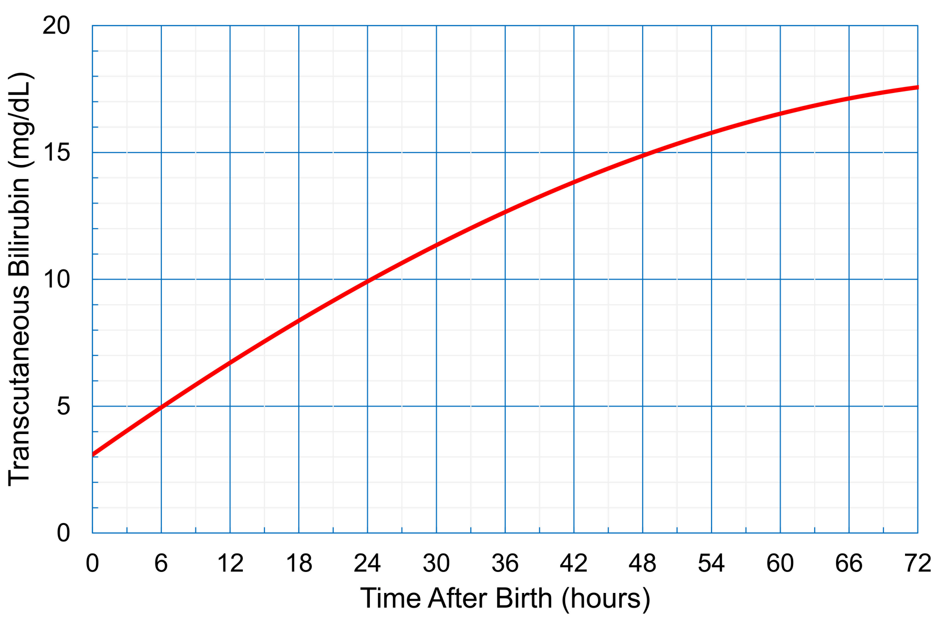

FIGURE 2
An hour-specific transcutaneous bilirubin nomogram for neonates in Myanmar (gestational age ≥ 35 weeks, birthweight > 2,000 g). This nomogram card was distributed to medical professionals for detecting neonatal hyperbilirubinemia.

nomogram). Baseline data were retrieved from the annual reports of the Central Women's Hospital Yangon for the years 2016 (16) and 2019 (17). Data on the date of birth, gestational age, sex, birth weight, mode of delivery, cause of hyperbilirubinemia, and days after birth, were recorded when ET was performed.

In Group 1, the management of hyperbilirubinemia was based on Kramer's rule; the neonates were checked three times a day (8 AM, 2 PM, and 8 PM, which were the timings for postnatal checkups) from day 0 to day 3 after birth, and they were treated according to the AAP guidelines using the total serum bilirubin (TSB) level determined during blood sampling.

In Group 2, TcB was measured by trained doctors using the JM-105 (Konica Minolta, Tokyo, Japan); the measurements were performed three times a day (8 AM, 2 PM, and 8 PM, which were the timings for postnatal checkups) from day 0 to day 3 after birth. The mid-sternum point on the chest of the neonates was chosen as the site of measurement, and the median value of the three measurements was plotted on the hour-specific TcB nomogram (**Figure 2**). If the value was higher than the 97.5th percentile of the nomogram, a physician collected a blood sample and followed the AAP guidelines for treatment (**Figure 1**). Treatment included phototherapy or ET.

Opt-out was implemented given the retrospective cohort study design, which precluded the acquisition of informed consent prior to the study. A notice on the research and opt-out policies was put up on the wall at the neonatal unit, for the guardians of the sample infants. This study was approved by the Ethical Committee Registry of the Faculty of Medicine Kagawa University (2021-225) and conducted in accordance with the principles described in the Declaration of Helsinki.

Statistical analysis

Categorical variables are presented as absolute numbers with percentages. Continuous variables are presented as medians with minimum and maximum values. The odds ratio of the number of ETs in Group 2 against the number of ETs in Group 1 was calculated using Microsoft Excel (Microsoft, Redmond, WA, United States).

Results

We initially included 15,254 neonates, of which 12,968 live-born neonates were categorized into Group 1 (2016), and 12,371 neonates, of which 10,090 were categorized into Group 2 (2019). Forty-six infants were treated with ET in Group 1, while only two infants were treated with ET in Group 2. The odds ratio for ET was 18.0 (Group 1 to Group 2; 95% confidence interval [CI]: 4.8–67.1; $p = 0.000$; **Table 1**). In Group 1, 46 cases received ET, of which 37 cases (80.4%) had G6PD deficiency as the cause of hyperbilirubinemia. In addition to G6PD deficiency, 11 out of 37 cases (29.7%) had an ABO incompatibility and one case had an Rh incompatibility. The etiology of six cases was unknown. **Figure 3** labels all 37 cases as "G6PD deficiency" requiring ET, regardless of the presence of an ABO or Rh incompatibility as the additional cause of hyperbilirubinemia. ET was performed between days 1 and 16 after birth, and day 2 was the median for ET administration in Group 1 (**Table 2** and **Figure 3**). Of the two ET cases in Group 2, one baby was born to an Rh-negative mother and the cord blood sample revealed a positive direct Coombs test and anemia. The second baby exhibited hemolytic jaundice of unknown etiology, with a family history of severe anemia and blood transfusion at birth in his elder sibling. Both babies in Group 2 underwent ET on day 0 (**Table 2** and **Figure 3**), and no baby with G6PD deficiency received ET. Serum bilirubin values at the time ET was administered were significantly higher in Group 1 than those in Group 2 (median: 23.0 and 16.8, respectively) (**Table 2**).

TABLE 1 Characteristics of the Group 1 and Group 2 neonates born at the Central Women's Hospital Yangon, Myanmar.

Characteristics	***n* (%)**	
	Group 1	**Group 2**
Study population	12,968	10,090
Hospitalized neonates	2,932 (22.6)*	2,049 (20.3)*
Sex (Male)	1,622 (55.3) **	1,119 (54.6) **
Delivery (VD: CS)	1,339 (45.7) : 1,593 (54.3)	901 (44.0) : 1,148 (56.0)
Hyperbilirubinemia	2,067 (70.5) **	1,169 (57.1) **
Phototherapy	2,020 (68.9) **	1,133 (55.3) **
ET	46 (1.6) **	2 (0.1) **

VD, normal spontaneous vaginal delivery; CS, cesarean section; ET, blood exchange transfusion cases which met the inclusion criteria for this study. *Divided by the number of study population. **Divided by the number of hospitalized neonates.

Discussion

Our study showed that the management of hyperbilirubinemia using TcB measurement and the nomogram significantly reduced the number of ETs, especially in patients with G6PD deficiency. This study is the first to demonstrate that the early detection of hyperbilirubinemia with TcB measurement is feasible in Myanmar and that the nomogram is very effective in managing neonatal hyperbilirubinemia. Indeed, this new screening method can be easily introduced in all neonatal units of hospitals in the country.

A major concern related to ET in Myanmar is the shortage of human resources. ET requires two doctors (one experienced and one unexperienced doctor), and two nurses (one to assist and one to run errands). Furthermore, neonatal patients need to be intensively cared for after ET. In addition, extra care will be needed if any serious complications occur, such as thromboembolism, necrotic-enteritis, arrhythmia, metabolic abnormalities, abnormal coagulation abnormalities, and infections (18). Therefore, the risk of consuming the limited human resources is a big challenge, especially given that human resources for health are below the WHO recommended level in Myanmar. Another concern is the limitations related to the screening of transfusion-transmissible infections. The only tests available are serology tests for malaria, hepatitis B, C, and HIV. CMV screening test, on the other hand, cannot be routinely performed. To avoid transfusion-related diseases, some prefer blood donation from family members. However, when the blood

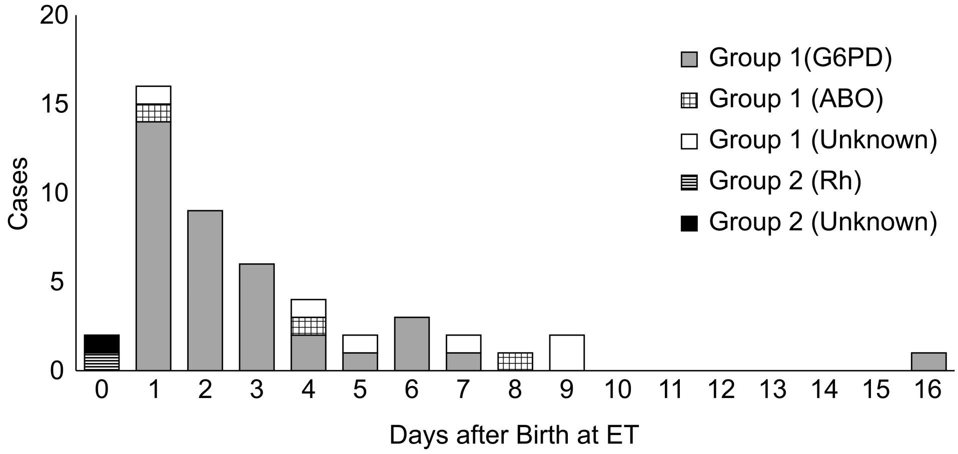

FIGURE 3
The number of cases that required ET according to the days after birth and causes of hyperbilirubinemia.

is not readily available in the blood bank, searching for the donor can be troublesome. Accordingly, the ET-related costs are very substantial in terms of human resources, medical care, and time. Therefore, if possible, ET should be prevented.

In our study, most patients that underwent ET had G6PD deficiency, which is common in malaria-endemic areas, such as tropical Africa and tropical and subtropical Asia (19). G6PD deficiency has been observed in the Myanmar population (20), with a prevalence rate of 6.1% (21). According to the AAP guidelines adopted in Myanmar, where screening for G6PD is not performed on a routine basis, neonatal assessment including the Beutler fluorescent spot test should be performed when neonates develop hyperbilirubinemia {bilirubin concentrations greater than the 95th percentile [150 µmol/L (8.8mg/dL)]} within the first 24 h of life (6). However, hyperbilirubinemia caused by G6PD deficiency is evident at 1–4 days of age, and its manifestation is similar to that of physiological jaundice (19), which is present in approximately 60% of the term newborns in the first week of life (22). This makes it difficult to suspect neonates with G6PD deficiency on day 0, thereby leaving them uncared for until hyperbilirubinemia is so obvious that they need ET. This fact explains why most neonates in this study were treated with ET on days 1 or 2 of life or latest on day 16 in 2016.

Central Women's Hospital, this study's site, had similar results to two previous hospital-based studies, which showed a similar incidence of G6PD deficiency in male infants (9%) (23, 24). Significant hyperbilirubinemia occurred in newborn neonates with G6PD deficiency (62.9%), whereas only 15.4% of severe cases were without G6PD deficiency; the ET rates were 3.2% and 0.2%, respectively. Not all G6PD-deficient patients had severe hyperbilirubinemia requiring ET during their hospital stay (23, 24). Since the incidence of G6PD deficiency is relatively high in this population, routine cord blood screening would be helpful to detect G6PD deficiency in Myanmar. Due to limited resources, however, the screening will not be routinely implemented. While male infants are to be tested for their G6PD status at Central Women's Hospital if they develop jaundice during their hospital stay, female infants are to be tested only if they need ET.

TABLE 2 Patient characteristics and causes of hyperbilirubinemia in neonatal cases requiring ET in Groups 1 and 2.

Characteristics	***n* (%), median (min-max)**	
	Group 1 (*n* = 46)	**Group 2 (*n* = 2)**
Sex (Male)	28 (60.9) : 18 (39.1)	2 (100) : 0 (0)
Delivery (VD: CS: V: F)	25 (54.3) : 19 (41.3) : 1 (2.2) : 1 (2.2)	0 : 1 (50) : 1 (50) : 0
BW	3,000 (2,100–4,400)	2,900 (2,500–3,300)
G6PD deficiency	37 (80.4)	0 (0)
Day at ET	2 (1–16)	0 (0–0)
SB values at ET	23.0 (17.3–33.0)	16.8 (6–13.8)

VD, normal spontaneous vaginal delivery; CS, cesarean section; V, vacuum; F, forceps; Day at ET, day after birth which blood exchange transfusion was administered; SB values at ET, serum bilirubin values at day ET was administered.

Thus, while the early detection of G6PD deficiency is difficult, the early detection of hyperbilirubinemia is feasible, particularly by following the screening method described in this study. Once hyperbilirubinemia is detected, irrespective of the cause, its timely and effective management by phototherapy, a non-invasive treatment, is possible. Consequently, early detection reduces the incidence of ET in patients with G6PD deficiency.

In 2019, two infants with hyperbilirubinemia were detected by our screening method and underwent ET on the day of birth. One baby had significant hyperbilirubinemia due to an

Rh incompatibility, and the other one was found to have hemolytic anemia at 6 h after birth. Interestingly, no patient with G6PD deficiency needed ET. The results demonstrated that our screening method could successfully detect all cases of significant hyperbilirubinemia and avoid unnecessary ET and its complications by providing early non-invasive interventions.

Our study, which analyzed a screening method involving TcB measurements, identified an effective early detection of neonatal hyperbilirubinemia. With Kramer's rule, TSB reached between 17.3 to 33.0 mg/dL when ET was administered, but TcB measurements could lead to early detection with TSB rising only between 6 to 13.8 mg/dL. Early detection leads to early treatment, which is a recommended convention as per the AAP guidelines. Indeed, we found that the number of cases requiring ET significantly differed between 2016 and 2019.

There is a high risk for healthcare malfunctioning and/or mismanagement in situations where new medical management protocols are introduced. However, our study showed that after the screening method was introduced, no technical or feasibility challenges were observed at the healthcare and medical centers. This is crucial for developing countries, such as Myanmar. Therefore, we recommend that this screening method be expanded to other hospitals in Yangon, provincial areas, and remote areas where medical resources are scarce. Such improvements in neonatal care may decrease the neonatal morbidity and mortality rates in Myanmar.

There are some limitations in our study that should be acknowledged. First, this was a single-center study. The hospital is a tertiary medical institution run by the government and is located in an urban area. Thus, it might be difficult to generalize the results to the entire country. Second, this was a retrospective study; accordingly, we could not prove causality between the screening method and the early treatment administered through phototherapy. Third, the reasons why some cases of hyperbilirubinemia led to ET are unknown because medical examinations are limited in Myanmar; routine examinations are limited to G6PD screening and ABO/Rh incompatibility, and do not include blood complete picture, bleeding and clotting profiles, cerebral hemorrhage, metabolic diseases, abnormalities on thyroid gland, or scrutiny on infection. Fourth, the contribution of this screening method to the early detection of severe neonatal hyperbilirubinemia 72 h after birth remains unclear, because the TcB nomogram for Myanmar neonates was applicable within 72 h of birth.

In conclusion, the management of hyperbilirubinemia with our screening method using an hour-specific TcB nomogram and TcB measurement is effective in reducing ETs in Myanmar neonates. Our study might contribute to a reduction in the medical burdens in neonatal care. Further research is urgently needed to examine the effectiveness of this screening method in other hospitals in different areas, especially where medical resources are scarce.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee Registry of the Faculty of Medicine Kagawa University (2021-225). Written informed consent from the participants or their legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

HS, SY, and YH conceptualized the study. HS, SY, NA, and TK designed the study. HS, SY, YH, TO, and ZH collected and analyzed the data. SY, NA, HO, and TK coordinated and supervised the data collection. HS drafted the initial manuscript. SY, YH, KK, SN, and TK critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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EDITED BY
Andrew Steenhoff,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Carolyn McGann,
Children's Hospital of Philadelphia,
United States
Lizelle Van Wyk,
Tygerberg Hospital, South Africa

*CORRESPONDENCE
Leshata Abigail Mapatha
noisemapatha@gmail.com

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A comparison of weight gain between HIV exposed uninfected and HIV unexposed uninfected infants who received KMC at Chris Hani Baragwanath Academic Hospital

Leshata Abigail Mapatha[1]*, Firdose Lambey Nakwa [1] and Mantoa Mokhachane [2]

[1]Department of Paediatrics and Child Health, Chris Hani Baragwanath Academic Hospital, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [2]Unit for Undergraduate Medical Education (UUME), School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Introduction: Kangaroo Mother Care (KMC) has been associated with improved growth in low birthweight infants and reduction in hypothermia, hypoglycaemia, apnoeas, sepsis, hospital stay, and mortality. The growth of HIV-infected children is poorer than those who are HIV-uninfected. There is paucity of data on weight gain in the HIV-exposed uninfected (HEU) infants compared to HIV-unexposed uninfected (HUU) infants receiving KMC.

Aim: This study compared the weight gain of HEU and infants HUU from admission to the KMC ward until 12 months corrected age (CA) follow-up visit.

Methods: Retrospective record review of the neonates admitted in KMC at Chris Hani Baragwanath Hospital over a 2-year period (2012–2013). The weight gain was assessed *via* weight velocity using the formula; weight/kg/day from admission to KMC to discharge, and g/ week at term, 3, 6 and 9- and 12-months (CA). The demographics were collected and analyzed using Statistica.

Results: Seventy-seven (129/166) percent of the mothers were HIV negative. HIV negative mothers were younger (25.9 vs. 31.6 years; $p = 0.000$) and had fewer pregnancies ($p = 0.02$). There was no difference between the gestational age (30.3 ± 2.53 vs. 30.8 ± 2.88 weeks; $p = 0.35$) and birthweight (1,345 g ± 234 vs. 1,314 g ± 209; $p = 0.47$) between HEU and HUU. There were no differences in the weight gain (23.83 g ± 12.2 vs. 23.22 g ± 15.2; $p = 0.83$) in KMC. There was no differences in weight gain at the different follow-up time points between the two groups.

Conclusion: Both HEU and HUU groups of infants showed reasonable weight gain despite maternal HIV status.

KEYWORDS

Kangaroo Mother Care (KMC), low birth weight (LBW), HIV, HIV exposed uninfected (HEU), HIV unexposed uninfected (HUU), weight gain (WG)

Background

In 2015, 20.5 million low birth weight (LBW) babies were born worldwide, which was 14.6% of all births (1). An estimated 2.4 million newborn babies died in their 1st month of life in 2020. Nearly half (47%) of all under-five deaths in 2020 occurred during the neonatal period (1). Prematurity (60–80%) and asphyxia (23%) are regarded as the commonest causes of the early neonatal deaths, whilst infections are the commonest cause of later neonatal deaths (2, 3). The lack of sophisticated Neonatal Intensive Care Unit (NICU) facilities contributes to the poor survival rate of premature infants in developing countries (4). Strategies to improve neonatal survival including introduction of antenatal steroids, surfactant administration, newer modes of ventilation, strict aseptic measures and Kangaroo Mother Care (KMC) have significantly increased survival of LBW infants in high middle income countries (HMICs) such as South Africa (5).

Kangaroo Mother Care, also referred to as Skin-to-Skin Contact (SSC) has become an important intervention for caring for LBW infants, particularly in high middle income countries (HMIC) where there is a high mortality and morbidity rate (6). The introduction of KMC in HMIC reduces the incidence of hypothermia, hypoglycemia, apnea, sepsis and hospital stay and promotes overall growth of head circumference, length and weight in the premature infant which correlates with brain volume and better cognitive ability later in life (7).

The adoption of the 2013 WHO recommendation of lifelong antiretroviral therapy (ART) for all HIV positive pregnant women (known as PMTCT option B+) in January 2015 by the South African government has significantly reduced the number of HIV exposed and infected (HEI) infants, leading to an era of HIV exposed uninfected (HEU) infants (8).

Historically weight, height, and head circumference have generally been lower in HIV exposed children than their unexposed counterparts (9). Weight gain was found to be a good predictor of neurodevelopmental outcome especially in extremely low birth weight (ELBW) neonates (10). High demands of health care services to improve growth in LBW infants who are also HIV exposed in South Africa make KMC a cost-effective way to prevent neonatal mortality in the health facilities (11).

Growth faltering has been well-described in the HEU population from studies in Sub-Saharan Africa (12–15). Some studies reported poorer weight gain in females and breastfed infants (14). A few South African studies have found no differences in weight gain between the HEU group as compared to HUU infants (16, 17). Advanced HIV disease, being exposed to ART *in utero* and exposure to certain anti-retroviral (ARV) drugs adversely affects weight gain (13, 15, 16). HIV exposure and ARV drugs have been associated with impaired immunity and placental insufficiency *via* endothelial function impairment (13–15, 18, 19). HIV replicates in the placenta during pregnancy and may affect the T-cytokine profile in the placenta and thus restrict fetal growth and development which might contribute to LBW in HIV exposed infants (20). There have been varying reports on the timing and the effect of different ART regimens on growth (12, 14).

The aim of this study was to compare the weight gain in HEU and HUU infants from admission to the KMC ward until 12 months corrected age at follow-up visit.

Methods

This study was conducted at Chris Hani Baragwanath Hospital, a tertiary hospital located in Soweto, South of Johannesburg, affiliated to the University of the Witwatersrand, South Africa. The unit had 175 neonatal beds and 25 KMC beds during the study period. The KMC ward is a facility for well-preterm born neonates who are waiting for weight gain and their mothers are encouraged to lodge in the ward to offer skin-to-skin care (SSC) to their babies throughout the day. During the study neonates weighing between 1,400 and 1,650 g and not requiring supplemental oxygen or intravenous fluids, were admitted to the KMC ward, provided their mothers were available to room-in with the baby. Mothers provided continuous SSC except when bathing or having meals, during which the babies were placed in the bassinets next to the mothers' bed. Length of stay was calculated from admission to KMC until discharge from KMC.

This is a retrospective study based on a review of medical records of LBW infants admitted in KMC over a 2-year period between 1st January 2012 and 31st December 2013. The study population included all HIV exposed and unexposed neonates weighing <1,650 g admitted to the KMC ward during the study period. All HIV positive neonates were excluded from the study (see Figure 1). Data was retrieved from medical records of the neonates that were admitted to the KMC and entered onto a datasheet. The data were entered onto an Excel Spreadsheet. Identifiers were kept separate from the neonatal and maternal demographics. A study number was assigned to the neonate, which was used to link the identifiers with the neonate's details. Neonatal records were divided into the HEU group and HUU group based on a documented maternal HIV status. All HIV exposed neonates (all neonates with positive maternal HIV test) had to have at least one documented polymerase chain reaction (PCR) result before being assigned to either the HEU or HUU group. At the time of the study, HIV in children was only tested at 6 weeks of age, 6 weeks post cessation of breast-feeding and 18 months of age (8).

Neonates were followed up at term [Corrected age (CA)–40 weeks], 3, 6, 9, and 12 months corrected age. To account for neonates not seen at the months mentioned above, a 1-month grace period on either side of the month was used for the infant's data to be included in the age group. For example, if the infant was seen at 4 months, the information was included in the 3-month age group. Information to be extracted from files included gestational age (GA), chronological age, corrected

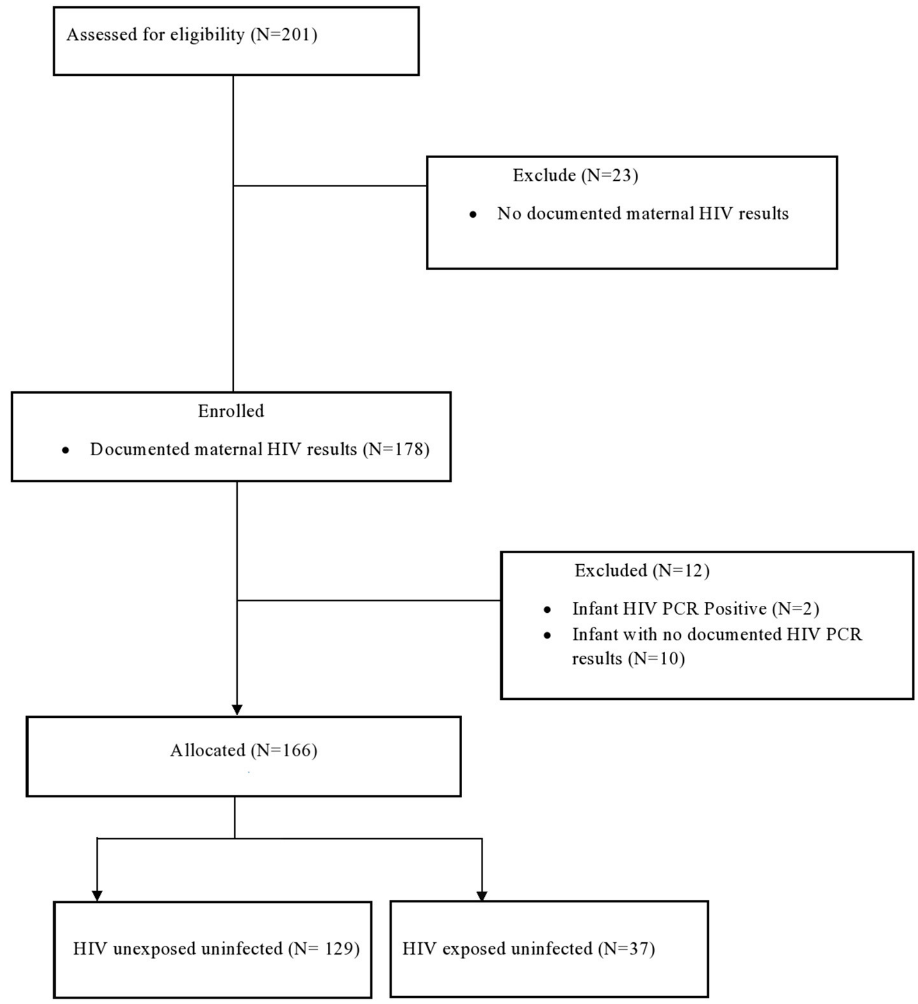

FIGURE 1
Flow diagram of neonates included in the study.

age (CA), birth weight, gender, HIV exposure, HIV status, mother's choice of feeds (breast fed or formula fed) supplements given (including FM85, a breastmilk fortifier), and the neonate's primary diagnosis (admitting diagnosis).

Each neonate's weekly weight was documented from date of admission into KMC ward until discharge. The discharge weight was 1,650 g at the time of the study in the KMC ward. Since participants were weighed daily during admission in KMC ward, only weights documented on Mondays and Thursdays were considered for the purpose of the study to avoid confusion. The median weight was calculated between the two weights. The patients were then weighed only on the day of follow up after discharge. To calculate the weight gained per week in g/week, the researcher used this formula: neonate's current weight in grams minus previous weight, divided by the number of weeks between the 2 weights. Adequate weight gain in KMC was set at 15 g/kg/day. For age 0–6 months this was 140–200 g/week and for those 6–12 months this was 85–140 g/week [1] (21).

Data analysis

The data were analyzed utilizing Statistica (Statsoft USA, version 13). Categorical data were reported as numbers and percentages and continuous variables as means and standard deviations, if the data were normally distributed; if not normally distributed the data were represented as medians and interquartile ranges. To compare the HEU and the HUU groups, the Student's-*t* tests was used for continuous variables

1 https://www.mayoclinic.org/healthy-lifestyle/infant-and-toddler-health/expert-answers/infant-growth/faq-20058037.

and the Chi-square test was used for categorical variables. A p-value < 0.05 was considered as significant.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of Witwatersrand (M180430). Permission to conduct the study was also obtained from the CHBAH hospital chief executive officer (CEO), the Pediatric and Neonatal Departmental Heads and National Department Health (NDoH).

Results

A total of 201 neonates with accessible medical records were included in the study. Of the 201 mother infant pairs, 178 (89%) mothers had a documented HIV status. Of the 178 infants, two were PCR positive and 10 had no PCR results, therefore HIV PCR negative results were available on 166 infants. A total of 166 mother- infant pairs were included in the study (Figure 1).

The baseline maternal characteristics were similar between the two groups (Table 1). Of the 166 mothers who were involved in the study, 129 (78%) were HIV negative and 37 (22%) were HIV positive. Of the 37 HIV positive mothers, 31 (83.7%) received highly active anti-retroviral treatment (ART), and one did not receive ART and the Prevention of Mother to Child Transmission (PMTCT) records were unknown in 6 (16.2%). Thirty-two (84.2%) infants born to HIV positive mothers received Nevirapine (NVP), three (8.1%) received zidovudine (AZT), and 25 (67.6%) received oral trimethoprim-sulfamethoxazole (Bactrim). Eighty-two (49%) infants were born *via* Caesarian section and 55 (33%) born *via* normal vaginal delivery (NVD). The booking, employment and marital status of mothers did not differ by HIV-exposure group (Table 1).

There were no significant differences between the gestational ages (30.3 $\pm$ 2.53 vs. 30.8 $\pm$ 2.88 weeks; $p = 0.35$) and birthweight (1,345.3 g $\pm$ 234 vs. 1 314.8 g $\pm$ 209.52; $p = 0.47$) in both groups. The majority of the infants involved in the study were female ($N = 89$, 54%). The incidence of RDS ($p = 0.44$) congenital pneumonia ($p = 0.766$), and necrotizing enterocolitis ($p = 0.89$) were not significant between the two groups. Eighty (63%) of the 129 HUU and 13 (35%) of the 37 HEU neonates had neonatal jaundice (NNJ) during their stay in the neonatal unit ($p = 0.03$). Length of stay in KMC was the same in both groups (13.2 $\pm$ 8.4 days in HUU vs. 14.0 $\pm$ 9.7 days in the HEU; $p = 0.83$; Table 2). There was no difference in mean weight gain in g/day in KMC and g/week at the different follow-up visits between the HUU and HEU (Table 3).

Discussion

KMC has many benefits to the low-birth-weight infant including improvement in weight gain and haemodynamic stability. Infants in KMC feed more frequently and this further promotes overall maternal-infant bonding. In the growing group of HIV exposed infants, this form of intervention becomes even more necessary to implement as this group of infants is already vulnerable to infections and poor growth. In our study, both HUU and HEU had adequate weight gain from term to 12 months CA. In Kenya, growth decline was documented in an HEU group after 6 months (22). This finding is not consistent with most of the literature. In a cohort study of HEU children from the pre-ART era in Zimbabwe, it was shown that HEU children had a 23% higher chance of stunting than the HUU children at 12 months of age (23). This is similar to studies done in Uganda and Zambia which both showed lower weight- for-age and lower height -for- age in the HEU vs. HUU infants.

In a more recent study done in Zimbabwe, a larger number of HEU were born preterm and had low birth weight when compared to the HUU infants. In the same study, the mean weight- for- age and length- for- age were significantly lower in HEU compared to HUU infants from birth to 16 weeks (24). A study in Cape Town has reported on lower birth weights in HEU neonates (13). The duration of ART antenatally may be a factor as this may affect the placenta, despite no differences found dependent on the timing of exposure. More studies are to be conducted investigating the ART regimens and the timing of exposure (13). To the contrary, another South African study found no differences in birthweight in HEU compared to HUU neonates, and longitudinal growth was greater in formula fed infants (14). The lack of a significant difference in weight gain between the HEU and HUU was an important finding. Maternal drugs such as ART and HIV prophylactic drugs received by the HEU infants such as NVP, AZT and trimethoprim-sulfamethoxazole do not affect growth in the HEU group (25). However, some studies showed poor growth in the HEU infants due to *in utero* exposure to HIV and maternal ART (26).

In South Africa, severe advanced maternal disease had poorer growth patterns whilst exposure to ART was associated with better weight gain (14). Pre-pregnancy maternal ART was associated with stunting and poor weight gain in a Kenyan study (15). These differences in studies may be related to the different regimens that are available in the various countries. Ejigu et al. in an Ethiopian cohort reported slower growth in HEU neonates, with growth faltering related to earlier exposure to ART, maternal disease and the type of ART (12). Our study did not have information on the maternal CD4 count nor viral load or the duration of maternal ART. More prospective studies regarding the timing of ART, the combination of ART and maternal disease severity are warranted to document the effects on growth patterns in our setting.

TABLE 1 Maternal demographics of neonates admitted to the KMC ward.

Characteristics	Total N (%) $N = 166$	HIV negative N (%) $N = 129$	HIV positive N (%) $N = 37$	p-value
Mean age (years)*	27.23 (±6.26)	25.9 (±2.5)	31.6 (±2.7)	0.00
Mean gravidity*	2.36 (±1.26)	2.17 (±1.17)	2.9 (±1.35)	0.02
Mean parity*	1.66 (±0.98)	2 (±1)	3 (±1)	0.00
Mode of delivery				
Cesarean section	82 (60)	65 (50)	17 (46)	0.83
NVD	55 (33)	40 (31)	15 (41)	
Missing	29 (18)	24 (19)	5 (13)	
Booked				
Yes	164 (99)	127 (98.5)	37 (100)	1.00
No	2 (1)	2 (1.5)	0	
Employed				
Yes	39 (24)	33 (26)	6 (16)	0.17
No	67 (40)	49 (38)	18 (49)	
Unknown	60 (36)	47 (36)	13 (35)	
Marital status				
Married	11 (7)	7 (5)	4 (11)	0.12
Single	114 (67)	89 (69)	25 (68)	0.28
Unknown	41 (26)	33 (26)	8 (21)	

*Mean (SD).
NVD, normal vaginal delivery; HIV, human immunodeficiency virus.

TABLE 2 Characteristics of neonates admitted to the KMC.

Characteristics	Total	HUU mean (SD)	HEU mean (SD)	p-value
Birth weight in grams	1,338.49 ±228)	1,345.3 (±234)	1,314.8 (±209)	0.47
Gestational age in weeks	30.4 (±2.61)	30.3 (±2.53)	30.8 (±2.88)	0.35
Apgar score				
1 min	7 (±1.9)	7 (±2)	7 (±2)	0.44
5 min	9 (±1.13)	9 (±1)	9 (±1)	0.15
Female	89 (54)	70 (55)	19 (51)	0.625
RDS*	128 (78)	101 (79)	27 (73)	0.44
Congenital pneumonia*	17 (10)	14 (11)	3 (8)	0.76
NEC*	29 (17)	23 (18)	6 (16)	0.89
NNJ*	93 (56)	80 (63)	13 (35)	0.03
Weight at admission to KMC (grams)	1,408.9 (±1.46)	1,402.0 (±145.12)	1,434.8 (±151.11)	0.3
Weight at discharge from KMC (grams)	1,674.5 (±100.89)	1,673.6 (105.19)	1,677.6 (85.60)	0.83
Length of stay in KMC in days	13.3 (±8.7)	13.2 (±8.4)	14.0 (±9.7)	0.64

*N (%).
HUU, HIV Unexposed Uninfected; HEU, HIV Exposed Uninfected; RDS, respiratory distress syndrome; NEC, necrotizing enterocolitis; NNJ, neonatal jaundice; KMC, Kangaroo Mother Care.

The incidence of developing RDS, congenital pneumonia and NEC was similar in both groups. This is similar to a study done in British Columbia, Canada which showed similar incidences of infectious respiratory and non-respiratory illnesses in HUU and HEU neonates. In this particular study the HEU were prone to acquiring infections requiring NICU admission compared to their HUU counterparts (27). The results in our study only focused on co-morbidities at admission to the neonatal unit, prior to admission to the KMC ward and no differences were noted between the two groups. These prior comorbidities did not affect weight gain in the KMC ward as shown in Table 3.

A higher proportion of HUU neonates had neonatal jaundice. This finding is in keeping with a study done in a hospital in Malawi, which showed a higher incidence of jaundice in HIV unexposed neonates as compared to the HIV

TABLE 3 Growth velocity in KMC and at term, 3, 6, 9, and 12 months.

Characteristic	HUU Means (SD)	HEU Means (SD)	*P*-value
Weight gain in KMC	$n = 91$	$n = 24$	0.83
g/day	23.83 (±12.2)	23.22 (±15.2)	
Term	$n = 86$	$n = 24$	0.44
g/week	205.4 (±74.7)	192.8 (±49.9)	
3 months	$n = 71$	$n = 22$	0.72
g/week	194.4 (±56.2)	189.6 (±49.7)	
6 months	$n = 48$	$n = 14$	0.91
g/week	173.5 (±46.6)	163.1 (±33.9)	
9 months	$n = 26$	$n = 15$	0.90
g/week	136.6 (±31.7)	135.5 (±21.3)	
12 months	$n = 20$	$n = 7$	0.81
g/week	117.9 (±22.6)	115.7 (±15.8)	

HUU, HIV Unexposed Uninfected; HEU, HIV Exposed Uninfected; KMC, Kangaroo Mother Care.

exposed neonates. One of the possible hypotheses for this finding as postulated by the authors is the use of drugs such as efavirenz, tenofovir, and lamivudine in pregnant and breast-feeding women as part of the prevention of mother-to-child transmission (PMTCT) programme in Malawi Efavirenz may act as a fetal liver enzyme inducer which helps in the conjugation of bilirubin thereby reducing the risk of jaundice in the HIV exposed infants (28).

South Africa is a poorly resourced HMIC country and thus most LBW infants do not have access to sophisticated neonatal care and equipment. This further highlights the important need for more KMC units in health care centers especially in the rural and semi-rural communities (7).

Maternal wellbeing is central to all aspects of infant's growth. Other factors which include nutritional, socioeconomic, health and environmental factors have an impact on childhood growth patterns. Although these factors were not assessed in this study, maternal height, body mass index (BMI) and education have been reported to contribute to growth faltering (15). An additional factor that may influence growth is family stress including other children left at home in poor socioeconomic circumstances and lack of support from hospital staff and family members (29). In Malawi maternal attitude to KMC was affected by mentorship, support, enthusiasm and training amongst health care workers and by family stress or support, especially by a lack of paternal support (30). These same factors also affected bonding between mother and infant. These factors are especially significant in mothers who are living with HIV due to the stigma associated with HIV (30).

The strength of our study is that it included a comparator group from the same community with similar socioeconomic status. Limitations of the study include that it was a single center study, and that we assessed growth using only weight gain at different ages and did not measure changes in length and head circumference. A further delineation of the maternal HIV status in terms of advanced disease, viral loads, CD 4 counts and ART regimens and when it was commenced were not investigated. The number of neonates and weights that were included at the different follow-up visits decreased over time.

Conclusion

Patients in this study gained weight at a normal rate with no difference in weight gain between HEU and HUU infants. Interventions promoting KMC should be implemented in both HEU and HUU infants as KMC is simple, effective and can be implemented with minimal resources. Future studies should assess changes in length and head circumference as well as weight gain. The finding of an increased incidence of jaundice in HEU infants as compared to the HUU infants should be explored in future studies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of the University of Witwatersrand. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Andrew Steenhoff,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Am Cilliers,
Chris Hani Baragwanath Hospital,
South Africa
Richard Onalo,
University of Abuja Teaching Hospital,
Nigeria

*CORRESPONDENCE
Li-Ping Shi
slping0222@zju.edu.cn

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Giant omphalocele associated pulmonary hypertension: A retrospective study

Tai-Xiang Liu, Li-Zhong Du, Xiao-Lu Ma, Zheng Chen and Li-Ping Shi*

Department of NICU, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Children's Hospital, Hangzhou, China

Background: Omphalocele is a common congenital defect of the abdominal wall, management of giant omphalocele (GO) is particularly for pediatric surgeons and neonatologists worldwide. The current study aimed to review and summarize the clinical features and prognosis in neonates with GO complicated with pulmonary hypertension (PH), which is associated with increased mortality, while in hospital.

Materials and methods: Medical records of infants with GO between July 2015 and June 2020 were retrospectively analyzed. The patients enrolled were divided into PH and non-PH groups based on the presence or absence of PH, and patients with PH were divided into death and survival groups based on survival status. Clinical characteristics and outcomes were compared between groups, respectively. The risk factors for PH were analyzed by binary logistic regression.

Results: In total, 67 neonates were identified as having GO and 24 (35.8%) were complicated with PH. Infants with PH were associated with intubation within 24 h after birth ($p = 0.038$), pulmonary dysplasia ($p = 0.020$), presence of patent ductus arteriosus (PDA; $p = 0.028$), a staged operation ($p = 0.002$), longer mechanical ventilation days ($p < 0.001$), oxygen requirement days ($p < 0.001$), parenteral nutrition (PN) days ($p < 0.001$), length of neonatal intensive care unit (NICU) or hospital stay ($p = 0.001$ and 0.002, respectively), and mortality ($p = 0.001$). The results of multivariable logistic regression analysis revealed that a staged operation was independently associated with PH. In addition, PH patients with lower birth weight, higher peak of pulmonary arterial systolic pressure, and refractory to pulmonary vasodilators (PVD) had increased mortality.

Conclusion: Pulmonary hypertension is a serious complication and significantly increases the mortality and morbidities in infants with a GO. In addition, early and serial assessment of PH by echocardiography should be a routine screening scheme, especially in the neonatal omphalocele population who required a staged surgical repair. Clinicians should be aware that infants with PH who had low weight, severe and refractory PH have a higher risk of death.

KEYWORDS

giant omphalocele, omphalocele, pulmonary hypertension, neonates, infants

Introduction

An omphalocele is a congenital abdominal wall defect that usually results in herniation of the abdominal organs, such as the liver, spleen, stomach, and intestine within a sac, and the condition has an estimated incidence of 1–3.8 per 10,000 life births (1, 2). Omphalocele can be generally classified into three types, i.e., small, giant, and ruptured, according to the size of the abdominal wall defect and/or its contents (3). Previous studies indicated that the size of an omphalocele, the increased viscero-abdominal disproportion, and the associated chromosomal or other important organ abnormalities are the main causes of death (4–6). Compared with a small omphalocele, infants with a giant omphalocele (GO) have a higher mortality rate of 20–25% (7, 8).

In recent years, clinicians have found that GO is associated with abnormalities in the pulmonary parenchyma and vasculature that lead to pulmonary hypoplasia and pulmonary hypertension (PH) (9–12). Moreover, PH is a severe and potentially fatal complication causing respiratory insufficiency, which requires aggressive ventilator support during the early postnatal period (13, 14). Based on these clinical questions, we carried out a retrospective analysis for characterizing the clinical features and prognosis of infants with a GO-associated PH.

Patients and methods

With the approval of the Institutional Review Board (IRB No. 2021-IRB-012), a retrospective study was performed on infants with congenital GO admitted to the neonatal intensive care unit (NICU) of the Children's Hospital, Zhejiang University School of Medicine between July 2015 and June 2020. The inclusion criteria for the study were all patients with a diagnosis of GO during the study period. Exclusion criteria were as follows: (1) small omphalocele; (2) ruptured omphalocele pre-admission; (3) congenital heart disease except for atrial septal defect (ASD), patent foramen ovale (PFO), patent ductus arteriosus (PDA), or small ventricular septal defect (VSD); and (4) patients with incomplete clinical data. The patients enrolled in the study were divided into PH and non-PH groups and patients with PH into death and survival groups according to the survival status (**Figure 1**). The patients' demographics, delivery information, cyst contents, associated abnormalities, neonatal care, surgical repair, respiratory and nutritional support requirements, and short-term prognosis of PH were recorded.

Definitions and interventions

We routinely used echocardiography to evaluate cardiac structure and pulmonary artery systolic pressure (PASP) in neonates with GO during the first week after birth and repeated once weekly in patients with clinical or echocardiographic evidence of PH or more frequently if clinically indicated, such as worsening of shunting, increased ventilator requirements, or other signs of clinical deterioration. PASP was estimated by measuring tricuspid regurgitation velocity (TRV) or calculated from the systemic pressure and the shunt pressure difference in the presence of intra-cardiac or extracardiac shunt. When there is no right ventricle outflow tract obstruction, PASP is equal to the right ventricular systolic pressure ($PASP = 4 \times (TRV_{max})^2 +$ right atrium pressure) (15). Generally, $TRV < 2.5$ m/s is considered normal (16). As the gold standard, right cardiac catheterization (RHC) should be performed when PH is clinically considered and cannot be accurately measured by echocardiography. PH was defined on echocardiography as the presence of tricuspid regurgitant jet with an estimated systolic pulmonary artery pressure (PAP) > 2/3 systemic systolic blood pressure and/or right-to-left or bidirectional flow at ductal and/or atrial level (17, 18). Once PH was diagnosed, pulmonary vasodilators (PVDs) were administered individually that included inhaled nitric oxide (iNO), treprostinil, milrinone, sildenafil, or bosentan.

The therapeutic effect of PVD on PH was echocardiographic improvement in PH. Echocardiographic improvement was defined as a 20% decrease in the absolute tricuspid regurgitation gradient or transform right-to-left or bidirectional flow into the left-to-right flow at ductal and/or atrial level between serial echocardiograms (19). Ineffectiveness was defined as without the above echocardiographic improvement or death occurred

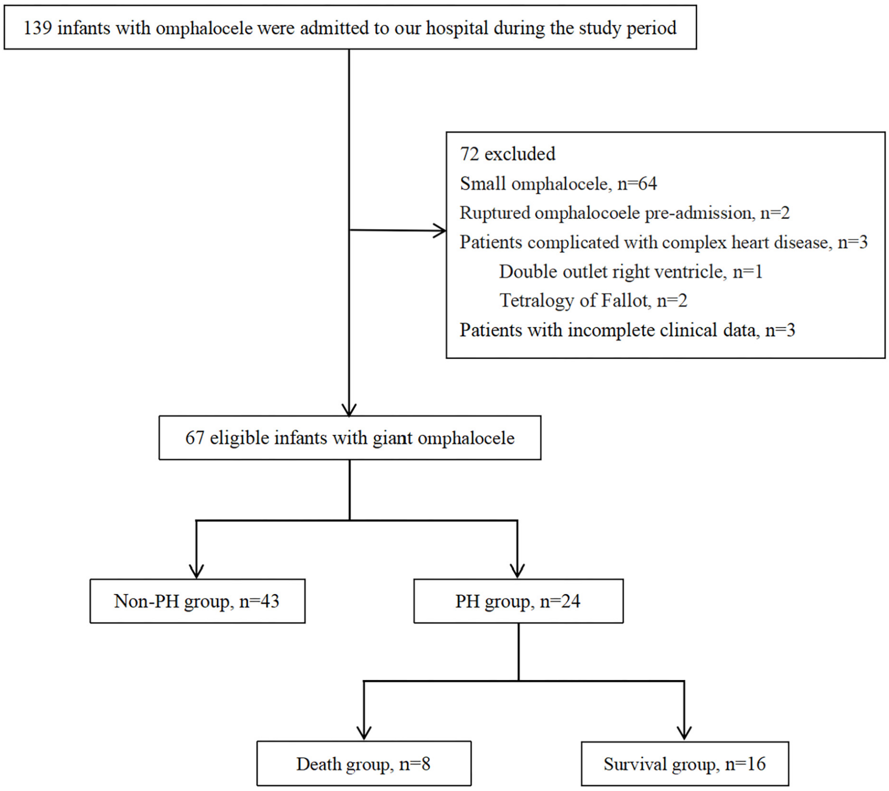

FIGURE 1
Flowchart of participants.

rapidly due to PH after treatment. Echocardiographic data were recorded, when possible, during the course of PVD treatment: time of introduction, 24–48 h after treatment, every other week after treatment and the disease worsen, or at the cessation of treatment or before discharge.

Giant omphalocele was defined as a large abdominal evisceration with a covering membrane containing more than 50–75% of the liver or an abdominal wall defect with a size of more than 5 cm (8). Pulmonary hypoplasia was characterized by a long, slight bell-shaped, and narrow chest with a marked reduction in lung volume and typical radiographic signs (20).

Patent ductus arteriosus was defined as the existence of persistent ductus arteriosus as demonstrated by echocardiography performed beyond 72 h of life in near-term and term infants (21). Respiratory system abnormalities included pulmonary hypoplasia, airway (tracheal bronchus and vascular loop), and diaphragm (diaphragmatic hernia and eventration). Digestive system abnormalities included intestinal malrotation, Meckel's diverticulum, and mesenteric hiatal hernia. Urogenital system abnormalities included indirect inguinal hernia and cryptorchidism.

In addition, we defined the liver and spleen as solid organs and the stomach, gallbladder, and intestine as hollow organs. Abdominal wall closure was performed by either disposable closure or staged repair that depends on the development of the abdominal cavity and the size of the omphalocele.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21 (IBM SPSS Inc., Chicago, United States). The Student's t-test and the Mann–Whitney U tests were used for continuous variables according to whether the data conformed to normal or non-normal distributions, respectively. X^2 test or Fisher exact test was used for categorical variables as appropriate. Data were presented as mean value ± standard deviation (SD), median with quartile range [M (Q1, Q3)], or percentages. All probability (p) values were two-tailed and a value < 0.05 was considered statistically significant.

In addition, we used the occurrence of PH as the dependent variable and variables with a statistically significant difference between the two groups (i.e., intubation within 24 h after birth, pulmonary hypoplasia, PDA, or a staged operation) and variables showing no statistical difference but reported in the previous literature to be related to PH (i.e., small for gestational age (SGA), perinatal asphyxia, or a solid/hollow organ in the sac) as the independent variables. The binary logistic regression analysis was performed using the forward logistic regression method, and the results are expressed as odds ratio (OR) with 95% CI.

The sample size was calculated by online software[1] and based on a retrospective literature review that concluded that in 48% of infants with omphalocele, the condition is complicated by PH. We hypothesized that 30% of infants had suffered from PH during hospitalization, considering the different definitions of PH, with 80% power, α = 0.05, and the 2-tailed test. The estimated total number of patients was 58, and the actual power was calculated to be more than 80%.

Results

A total of 67 infants with GO met the inclusion criteria and were identified in the retrospective analysis. In total, 35.8% (24/67) of infants presented echocardiographic evidence meeting the criteria for a diagnosis of PH, while the remaining 64.2% (43/67) did not have evidence of PH.

Compared with the non-PH group, the PH group had a higher proportion of intubation within 24 h after birth ($p = 0.038$), pulmonary hypoplasia ($p = 0.020$), a PDA ($p = 0.028$), and a staged operation ($p = 0.002$). The other clinical characteristics were not significantly different between the two groups ($p > 0.05$; **Table 1**). The results of binary regression analysis showed that the staged operation was independently associated with PH in infants with a GO ($p = 0.010$; **Table 2**).

In terms of clinical outcome indicators, PH was found to be significantly associated with the duration of mechanical ventilation ($p < 0.001$), oxygen requirement days ($p < 0.001$), length of NICU stay ($p = 0.001$), and length of hospital stay ($p = 0.002$). In addition, the requirement for supplemental oxygen at home in the PH group was higher than that in the non-PH group (20.8 vs. 7.0%), although this difference was not statistically significant ($p > 0.05$). In addition, digestive system abnormalities were diagnosed in the majority of patients in both patients' cohorts, with a requirement for parenteral nutrition (PN) support lasting for 31 d in the PH group and 14 days in the non-PH group, respectively ($p < 0.001$). It should be noted that mortality was also increased significantly in the PH group ($p = 0.001$; **Table 3**).

Table 4 provides a description of the clinical characteristics of infants with PH in the death and survival groups. Patients in the death group had a lower birth weight ($p = 0.019$) and a higher systolic PAP ($p = 0.003$). In terms of treatment, 1 patient suffered from sudden death due to PH crisis without PVD therapy, while 19 infants received two or more types of PVD and 4 underwent PDA ligation. As for the efficacy of the drug, the patients in the death group had a worse response to the PVD therapy ($p = 0.004$).

1 https://www.biostats.cn/samplesize/

TABLE 1 Comparison of the baseline characteristics of the study cohort by the presence of PH.

Variables	PH group (*n* = 24)	Non-PH group (*n* = 43)	*P*-value
Male gender	16 (66.7%)	20 (46.5%)	0.113
Gestational age (wk)	38 (36.3–38.3)	38 (36.1–38.7)	0.942
Birth weight (g)	2834 ± 690	2693 ± 581	0.378
SGA	2 (8.3%)	7 (16.3%)	0.589
Perinatal asphyxia	8 (33.3%)	6 (14%)	0.061
Intubation within 24 h after birth	6 (25%)	2 (4.7%)	0.038*
Solid organ in the sac	24 (100%)	43 (100%)	NA
Hollow organ in the sac	19 (79.2%)	27 (62.8%)	0.166
Respiratory system abnormalities	21 (87.5%)	27 (62.8%)	0.031*
Pulmonary hypoplasia	21 (87.5%)	26 (60.5%)	0.020*
Tracheal bronchus	2 (8.3%)	0 (0%)	0.125
Vascular loop	2 (8.3%)	0 (0%)	0.125
Diaphragmatic hernia and eventration	2 (8.3%)	1 (2.3%)	0.290
Digestive system abnormalities	20 (83.3%)	32 (74.4%)	0.401
Intestinal malrotation	20 (83.3%)	29 (67.4%)	0.159
Meckel's diverticulum	3 (12.5%)	4 (9.3%)	0.695
Gallbladder agenesis	2 (8.3%)	3 (7%)	>0.999
Mesenteric hiatal hernia	0 (0%)	1 (2.3%)	>0.999
Urogenital system abnormalities	6 (25%)	4 (9.3%)	0.149
Indirect inguinal hernia	5 (20.8%)	3 (7%)	0.124
Cryptorchidism	2 (8.3%)	2 (4.7%)	0.614
Beckwith-wiedemann syndrome	1 (4.2%)	1 (2.3%)	>0.999
PDA	7 (29.2)	3 (7%)	0.028*
Age at surgery (d)	2 (2–5)	2 (1–3)	0.144
Staged operation	7 (29.2)	1 (2.3)	0.002

IQR, interquartile range; PDA, patent ductus arteriosus; PH, pulmonary hypertension; SD, standard deviation; SGA, small for gestational age; NA, not applicable. *Represents statistically significant, $p < 0.05$.

TABLE 2 Logistic regression analysis of risk factors of GO-associated PH.

Variable	β	*P*-value	OR	95% CI
Staged operation*	2.850	0.010	17.294	1.975–151.424
Constant	−0.904	0.002	0.405	

CI, confidence interval; GO, giant omphalocele; OR, odds ratio; PH, pulmonary hypertension. *Represents statistically significant, $p < 0.05$.

TABLE 3 Comparison of clinical outcomes of the study cohort by the presence of PH.

Variables	PH group (n = 24)	Non-PH group (n = 43)	P-value
Duration of mechanical ventilation (days)	11 (5–42)	3 (1–6)	<0.001*
Oxygen requirement days (days)	39 (21–62)	15 (6–31)	<0.001*
Requirement for supplemental oxygen at home	5 (20.8%)	3 (7%)	0.065
PN days (days)	31 (22–48)	14 (10–19)	<0.001*
Nasal feeding home	1 (4.2%)	1 (2.3%)	>0.999
Length of NICU stay (days)	28 (14–51)	11 (8–20)	0.001*
Length of hospital stay (days)	40 (24–65)	19 (15–29)	0.002*
Death	8 (33.3%)	1 (2.3%)	0.001*

IQR, interquartile range; NICU, neonatal intensive care unit; PH, pulmonary hypertension; PN, parenteral nutrition. *Represents statistically significant, $p < 0.05$.

TABLE 4 Clinical characteristics of death and survival groups in infants with PH.

	Death group (n = 8)	Survival group (n = 16)	P-value
Gestational age (wk)	37 (32.7–38.1)	38 (37.5–38.6)	0.114
Birth weight (g)	2379 ± 787	3061 ± 525	0.019*
Intubation within 24 h after birth	3 (37.5%)	3 (18.8%)	0.362
Time of diagnosis of PH (days)	8 (1–78)	5 (3–7)	0.516
PH diagnosed within 7 days after birth	4 (50%)	12 (75%)	0.363
PASP (mmHg)	86.4 ± 21.7	61.3 ± 15.4	0.003*
Systolic SBP (mmHg)	76.5 ± 9.9	71.3 ± 7.1	0.152
Types of PVD			
Single type of PVD	0 (0%)	4 (25%)	0.273
Two types of PVD	3 (42.9%)	7 (43.8%)	>0.999
Three or more types of PVD	4 (57.1%)	5 (31.3%)	0.363
Therapeutic effect of PH			
Improvement	3 (42.9%)	16 (100%)	0.004*
Ineffectiveness	4 (57.1%)	0 (0%)	0.004*
Duration of PVD (days)	21 ± 36	38 ± 28	0.257
PDA	2 (25%)	5 (31.3%)	>0.999
PDA ligation	0 (0%)	4 (25%)	0.262

IQR, interquartile range; PASP, pulmonary arterial systolic pressure; SBP, systemic blood pressure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVD, pulmonary vasodilators; SD, standard deviation. *Represents statistically significant, $p < 0.05$.

Discussion

This study reviewed and summarized the clinical data of infants with GO complicated with PH who were admitted to a national regional medical center in China. We found that infants with PH have a higher proportion of intubation within 24 h after birth, pulmonary hypoplasia, presence of a PDA, a staged operation for an omphalocele and were associated with the requirement for respiratory support, prolonged hospital stay, and increased mortality. The results of regression analysis showed that a staged operation was an independent risk factor for PH. In addition, infants with lower birth weight, higher degree of systolic PAP, and refractory to PVD therapy were more likely to increase mortality.

Giant omphalocele-associated PH has been reported to be a severe, even potentially life-threatening clinical complication with high morbidity and mortality in previous studies (22), similar to the results of our study. However, the pathogenesis of PH in patients with GO remains unclear. At present, it is considered that it may be related to pulmonary dysplasia, pulmonary vascular smooth muscle remodeling, and abnormal vascular tension (11). This was confirmed by a case of omphalocele complicated with severe PH, with the final pathological diagnosis consistent with congenital alveolar capillary dysplasia and characterized by a fatal developmental lung disorder observed in neonates and infants (9). In addition, prenatal ultrasound and magnetic resonance imaging (MRI) had been applied to assess the total lung volume and pulmonary hypoplasia in infants with an omphalocele, suggesting that the lung volume and gas exchange area were significantly reduced (23–25). Animal experiments further indicated that an abdominal wall defect does in fact affect the differentiation between type I alveolar epithelial cells and type II alveolar epithelial cells (26). Our study found that the pulmonary dysplasia diagnosed by typical radiographic signs was far more common in infants with PH who suffered from a higher proportion of the requirement for ventilator and oxygen support, which suggested that GO-associated PH is indeed a certain degree of primary pulmonary developmental abnormalities.

Unlike many other diseases, an optimal surgical repair approach to the omphalocele remains controversial and frequently requires multi-disciplinary consideration of various factors, such as the size of abdominal wall defect, presence of herniated solid organs, presence of associated abnormalities, and the severity of associated pulmonary hypoplasia and PH (27, 28). Early primary closure of the defect may lead to a sudden increase in intra-abdominal pressure and abdominal compartment syndrome, which presents as acute kidney injury, respiratory, and hemodynamic deterioration in those GO patients with a small abdominal cavity (29, 30). In our study, infants with a GO required staged surgical closure of the defect, which was significantly correlated with PH, possibly due to the potential small abdominal cavity and a high viscero-abdominal disproportion, which may modify diaphragm function and mobility, causing secondary pulmonary dysplasia and respiratory compromise (10).

Pulmonary hypertension was considered to be independently associated with mortality in patients with omphalocele (11–13). Our study further confirmed that patients with PH who had lower birth weight, higher PASP, and refractory to PVD therapy were having increased mortality. As for treatment, combined use of PVD with different sites of action should be considered as a consequence of the multiple mechanisms involved in the pathogenesis of PH (31, 32). We preferred to administer iNO or remodulin when infants were in a critical condition, followed by oral sildenafil and/or bosentan for further treatment. Significantly, PDA is a common cardiovascular defect characterized by a large volume of transductal left-to-right shunt that may increase pulmonary blood flow and the left-side heart volume loading, causing a further increase in PAP and cardiac insufficiency (21). In our study, the symptoms that presented as persistent ventilator or oxygen dependence in four patients diagnosed with PH accompanied by symptomatic PDA were partially alleviated after transthoracic PDA ligation, despite a lack of consensus regarding the indication for PDA surgical intervention in this population (33).

Limitations

First, the sample capacity of the study was hampered by excluding small-sized omphalocele. Second, we only diagnosed pulmonary dysplasia through typical radiological signs rather than lung biopsy to determine the development of pulmonary parenchyma and vasculatures. Third, the present study lacks follow-up on the long-term prognosis that includes pulmonary and neurological function in patients. Finally, the study lacks innovation to a certain extent, because the genetic and molecular biological analyses were not performed in participants.

Conclusion

In conclusion, PH is a serious complication and significantly increases the mortality and morbidities in infants with a GO. Early and serial assessment of PH by echocardiography should be a routine screening scheme, especially in the neonatal omphalocele population who required a staged surgical repair. Furthermore, clinicians should be aware that infants with PH who had low weight, severe and refractory PH, have a higher risk of death.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Medical Ethics of the Children's Hospital, Zhejiang University School of Medicine. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

T-XL and L-PS were designed by the ideas and protocol of this study. T-XL, ZC, and X-LM were obtained by medical records. T-XL completed the manuscript and worked for the statistical analysis. L-PS and L-ZD revised the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Britt Nakstad,
University of Botswana, Botswana

REVIEWED BY
Clement Ezechukwu,
Nnamdi Azikiwe University, Nigeria
Susan Coffin,
University of Pennsylvania,
United States

*CORRESPONDENCE
Gloria Mutimbwa Siseho
2520821@myuwc.ac.za

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Monitoring healthcare improvement for mothers and newborns: A quantitative review of WHO/UNICEF/UNFPA standards using Every Mother Every Newborn assessment tools

Gloria Mutimbwa Siseho[1,2]*, Thubelihle Mathole[1] and Debra Jackson[1,3]

[1]University of the Western Cape, Cape Town, South Africa, [2]United Nations Children's Fund (UNICEF), Windhoek, Namibia, [3]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Assessment tools with the ability to capture WHO/UNICEF/UNFPA standard quality-of-care measures are needed. This study aimed to assess the ability of Every Mother Every Newborn (EMEN) tools to capture WHO/UNICEF/UNFPA maternal and newborn quality improvement standard indicators.

Methods: A quantitative study using the EMEN quality assessment framework was applied. The six EMEN tools were compared with the WHO/UNICEF/UNFPA maternal and newborn quality improvement standards. Descriptive statistics analysis was carried out with summaries using tables and figures.

Results: Overall, across all EMEN tools, 100% (164 of 164) input, 94% (103 of 110) output, and 97% (76 of 78) outcome measures were assessed. Standard 2 measures, i.e., actionable information systems, were 100% (17 of 17) completely assessed by the management interview, with 72% to 96% of standard 4–6 measures, i.e., client experiences of care, fulfilled by an exit interview tool.

Conclusion: The EMEN tools can reasonably measure WHO/UNICEF/UNFPA quality standards. There was a high capacity of the tools to capture enabling policy environment and experiences of care measures not covered in other available tools which are used to measure the quality of care.

KEYWORDS
assessment tools, monitoring, standards, statements, measures, childbirth, healthcare improvement

Introduction

There is an increasing demand to improve quality care as health facility deliveries increase in low- and middle-income countries (LMIC). The time of birth poses the highest risk of dying for newborns, with an occurrence of 2.5 million stillbirths and 2.6 million neonatal deaths occurring in 0–28 days of life annually (1–4). The Sustainable Development Goals for child health will be difficult to meet without a strategic focus to improve quality care around childbirth (1, 2).

Improving the quality of healthcare around the time of birth will reduce maternal and newborn mortality and stillbirths by over half (2), as the provision of high quality of care during childbirth will prevent most intrapartum stillbirths, 61% of neonatal deaths, and half of the maternal deaths (2). The increase in facility deliveries in LMIC may not result in reduced maternal and newborn deaths if the quality of care is also not improved (5, 6).

WHO/UNICEF/UNFPA quality-of-care standards

In response to the increasing demand to prioritise the quality of care at birth, WHO/UNICEF/UNFPA developed frameworks (**Supplementary Figure 1** and **Supplementary Table 1**) and released standards (**Supplementary Table 2**) for improving quality care for maternal and newborn healthcare (5, 6). The WHO/UNICEF/UNFPA quality standards include eight standards across two dimensions plus cross-cutting areas of quality The first dimension of quality is 'provision of care' with (1) evidence-based care practices, (2) actional information systems, and (3) functional referral systems. The second dimension is 'experiences of care' including (4) effective communication, (5) respect and dignified care, and (6) emotional support. The last two are 'cross-cutting' and include (7) competent, motivated staff and (8) availability of essential physical resources. The standards are further divided into 31 quality statements. The quality statements are then classified into 352 quality measures. The quality measures are subdivided into 164 input, 110 output/process, and 78 outcome measures. These standards along with the accompanying monitoring framework were published in 2017. While monitoring indicators have been defined for the maternal and newborn period, a specific tool to measure the WHO/UNICEF/UNFPA quality-of-care standards does not exist.

WHO/UNICEF Every Mother Every Newborn assessment tool: Measuring quality of care

In response to the global initiatives on quality of care, United Nations Children's Fund (UNICEF) developed nine EMEN quality standards in 2014 (**Supplementary Table 1**) as a precursor to the 2017 WHO/UNICEF/UNFPA maternal and newborn standards of care. While similar, the 2017 WHO and the initial 2014 UNICEF standards do differ (**Supplementary Table 2**). First, the EMEN standards include a standard around antenatal care, which is not included in the 2017 standards. Also, in the EMEN tool, there are nine standards that focus on the quality of care during delivery and within 24 h of birth for the mother and newborn (6). The EMEN standards are as follows: (1) Evidence-based safe care is provided during labour and childbirth, (2) evidence-based safe postnatal care is provided for all mothers and newborns, (3) human rights are observed, and the experience of care is dignified and respectful for every woman and newborn, (4) a governance system is in place to support the provision of quality maternal and newborn care, (5) the physical environment of the health facility is safe for providing maternal and newborn care, (6) essential medications, supplies, functional equipment, and diagnostic services are available for maternal and newborn care, (7) qualified and competent staff are available in adequate numbers to provide safe, consistent, and quality maternal and newborn care, (8) health information systems are in place to manage patient clinical records and service data, and (9) services are available to ensure the continuity of care for all pregnant women, mothers, and newborns.

Based on these earlier 2014 standards, the EMEN quality-of-care assessment tools (7) were developed between 2014 and 2016 by harmonising existing global tool(s) at that time. The harmonised tools included WHO Service Availability and Readiness Assessment (SARA), U.S. Agency for International Development (USAID), the Service Provision Assessment (SPA), and EmOC assessment tool for Averting Maternal Death project in Columbia University (AMDD) (8). Jointly, between 2014 and 2016, three countries (7, 8) supported by UNICEF selected relevant questions, pretested them, and organised them by EMEN standards (**Supplementary Table 1**) into a set of EMEN (unified) tools. The theoretical framework of the EMEN tool (**Supplementary Table 3**) has strengths in covering all areas of quality care from inputs, outputs/process, and outcomes to the documentation of clientele care provisions (8). The three countries which tested the EMEN tools found the existence of policies, infrastructure, and staff willingness to provide respectful maternity care (8). They also suggested that the EMEN tools assessed facility readiness for implementing the quality-of-care standards for improving maternal and newborn care (8).

Rationale for the study

Developing strategies to improve quality care during childbirth will be difficult to achieve without the availability of unified quality assessment tools. The EMEN assessment tools exist and have been used to assess and implement quality care in three countries (8–10). However, confirming the ability of the final tool published by UNICEF in 2016 captures the 2017 WHO/UNICEF/UNFPA quality improvement standards for maternal and newborn care is needed. The ability of the EMEN tool to capture quality of care during childbirth is not documented elsewhere. Thus, this study objective is to determine the capacity of 2016 EMEN assessment tools in measuring the 2017 WHO/UNICEF/UNFPA quality improvement standard indicators for maternal and newborn care (Supplementary Table 2). The aim is to document and map the ability of the EMEN tool prior to its administration in the field. The results of this study are further crucial in addressing identified gaps and recommendations from previous studies (11–13).

Materials and methods

Although the EMEN tool was pretested and used in three UNICEF-supported countries, for this study, pre-assessment and mapping of the capacity of the EMEN tool to gauge the quality of care around childbirth were necessary prior to data collection. The aim was to determine and document the capacity of the EMEN tool/questionnaires in capturing WHO/UNICEF/UNFPA quality standard measures around childbirth before data collection. To document and map the capacity of the EMEN tool/questionnaires, the following steps were applied. Step 1: Two documents were reviewed and gauged against each other: the first document is the WHO standards for improving the quality of maternal and newborn care in health facilities and (5) the second is the UNICEF EMEN facility training manual for assessing the implementation of the standards for improving the quality of maternal and newborn care in health facilities (7). Step 2: A table to match the eight WHO quality standards against the six EMEN tool/questionnaires was created. Each quality standard has two or three quality statements, except for standard 1, which has 13 quality statements, making a total of 31 quality statements. Each of the quality statements comprised six to eight quality measures on the elements of care (inputs, output, and outcome), resulting in 352 quality measures. Each of the six EMEN tool/questionnaires comprises a range of 113 questions (for management and exit interviews) to 197 questions for the medical record review, resulting in a total of 869 questions. Step 3: Each of the 869 questions from all the six EMEN questionnaires against the 352 quality measures within the 31 quality statements under the eight quality standards was populated and matched (Supplementary Appendix A pp. 1–284, Supplementary material). A quality measure was considered a match if one question and/or a wording from any of the EMEN questions matched with a quality measure (Supplementary Appendix A pp. 1–284, Supplementary material). Step 4: A final matrix table (Supplementary Appendix A pp. 1–284) indicating all the questions per EMEN questionnaires (in columns) gauged against each of the WHO standards, statements, and/or measures (in rows) was created. The last page of the Supplementary Appendix A table also shows which of the WHO quality measures were not assessed by any of the six EMEN questionnaires. The matrix table (Supplementary Appendix A pp. 1–284), though large, represents comprehensive summary results of this study by clearly depicting all questions/materials and quality measures assessable by the EMEN tool. To simplify the assessed elements, we further analysed, described, and presented short versions of Supplementary Appendix A 1–284 in Supplementary Figure 1, Supplementary Table 4, and Figures 2, 3.

The mapping of each element and/or question in the EMEN questionnaires to the relevant quality standards, statements, and

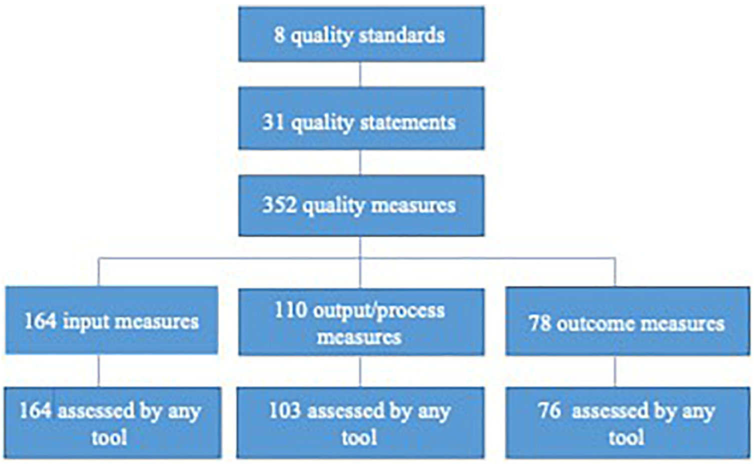

FIGURE 1
WHO/UNICEF/UNFPA quality of care standards, statements and measures.

measures in the WHO/UNICEF/UNFPA framework was carried out by the first author. The second and third authors performed the review of the analysed documents, tables, and figures to ensure alignment or agreement.

Description of the materials/tools

The EMEN quality assessment tools are designed to narrate a story of care provision through inputs, outputs/process, and outcomes around the time of birth. The tool consists of six structured questionnaires: (1) facility physical, structural, and functional readiness form 1 (F1:PSFR), (2) facility management interview form 2 (F2:MI), (3) facility staff interview with vignettes form 3 (F3:SIV), (4) facility observation of provider–client interactions and care provision form 4 (F4:OPCIC), (5) client medical records review form 5 (F5:CMRR), and (6) women's exit interview and companion perceptions of care form 6 (F6:WEICPC).

F1:PSFR assesses space, services, equipment, drugs, and supplies used to provide quality care. F2:MI reviews overall facility policies, guidelines, and staff rotation. F3:SIV determines formal and refresher trainings received by staff providing maternal and newborn care and performance of signal functions. F3:SIV also contains vignettes to test staff knowledge and practices. F4:OPCIC follows up a woman presenting in labour as she navigates through the various areas in the facility. F4:OPCIC provides real-time data on care provision and highlights gaps identified. F5:CMRR examines the client's medical record to capture the quality of data on care provision; assess the quality-of-care content including partograph review, and observe the caesarean section; and also collects data on

TABLE 1 WHO/UNICEF/UNFPA quality standards and EMEN quality measures and tool.

Eight WHO/UNICEF/UNFPA standards, nine EMEN quality measures, by six EMEN tool.

WHO/UNICEF/UNFPA Standards of care	EQUIVALENT EMEN Quality measures	Assessable EMEN questionnaire per Standards
Standard 1: Every woman and newborn receives routine, evidence-based care and management of complications during labour, childbirth, and the early postnatal period, according to WHO guidelines.	1. Evidence-based safe care is provided during labour and childbirth. 2. Evidence-based safe postnatal care is provided for all mothers and newborns. 5. The physical environment of the health facility is safe for providing maternal and newborn care.	F1.Physical, structural, and functional readiness; F2. Management Interviews; F3. Staff interviews; F4. Observations of provider-client interactions; F5. Medical record review; F6. Women exit interviews.
Standard 2: The health information system enables the use of data to ensure early, appropriate action to improve the care of every woman and newborn.	8. Health information systems are in place to manage patient clinical records and service data	F1.Physical, structural, and functional readiness; F2. Management Interviews; F3. Staff interviews; F4. Observations of provider-client interactions; F5. Medical record review; F6. Women exit interviews.
Standard 3: Every woman and newborn with condition(s) that cannot be dealt with effectively with the available resources is appropriately referred.	9. Services are available to ensure continuity of care for all pregnant women, mothers, and newborns.	F1.Physical, structural, and functional readiness; F2. Management Interviews; F3. Staff interviews; F4. Observations of provider-client interactions; F5. Medical record review; F6. Women exit interviews.
Standard 4: Communication with women and their families is effective and responds to their needs and preferences.	3. Human rights are observed and the experience of care is dignified and respectful for every woman and newborn	F1.Physical, structural, and functional readiness; F2. Management Interviews; F3. Staff interviews; F4. Observations of provider-client interactions; F5. Medical record review; F6. Women exit interviews.
Standard 5: Women and newborns receive care with respect and preservation of their dignity.	3. Human rights are observed and the experience of care is dignified and respectful for every woman and newborn	F1.Physical, structural, and functional readiness; F2. Management Interviews; F3. Staff interviews; F4. Observations of provider-client interactions; F5. Medical record review; F6. Women exit interviews.
Standard 6: Every woman and her family are provided with the emotional support that is sensitive to their needs and strengthens the woman's capability.	3. Human rights are observed and the experience of care is dignified and respectful for every woman and newborn	F1.Physical, structural, and functional readiness; F2. Management Interviews; F3. Staff interviews; F4. Observations of provider-client interactions; F5. Medical record review; F6. Women exit interviews.
Standard 7: For every woman and newborn, competent, motivated staff are consistently available to provide routine care and manage complications.	7. Qualified and competent staff are available in adequate numbers to provide safe, consistent, and quality maternal and newborn care. 4. A governance system is in place to support the provision of quality maternal and newborn care	F1.Physical, structural, and functional readiness. F2. Management Interviews. F3. Staff Interviews with Vignettes. F4.Observation of Provider-Care Interactions. F5. Medical Record Review. F6. Women Exit Interviews
Standard 8: The health facility has an appropriate physical environment, with adequate water, sanitation and energy supplies, medicines, supplies and equipment for routine maternal and newborn care and management of complications.	5. The physical environment of the health facility is safe for providing maternal and newborn care. 6. Essential drugs, supplies and functional equipment, and diagnostic services are consistently available for maternal and newborn care.	F1.Physical, structural, and functional readiness. F2.Management Interviews. F3.Staff Interviews with Vignettes. F4.Observation of Provider-Care Interactions. F5. Medical Record Review. F6. Women Exit Interviews

outcomes. Women's exit interview (F6. WEICPC) assesses the client at the time of discharge for their perception of quality care provided to them during their hospital stay. F6:WEICPC obtains data from the time of admission, through labour, childbirth, and postnatal care to the time of discharge home. Also, F6:WEICPC addresses examinations,

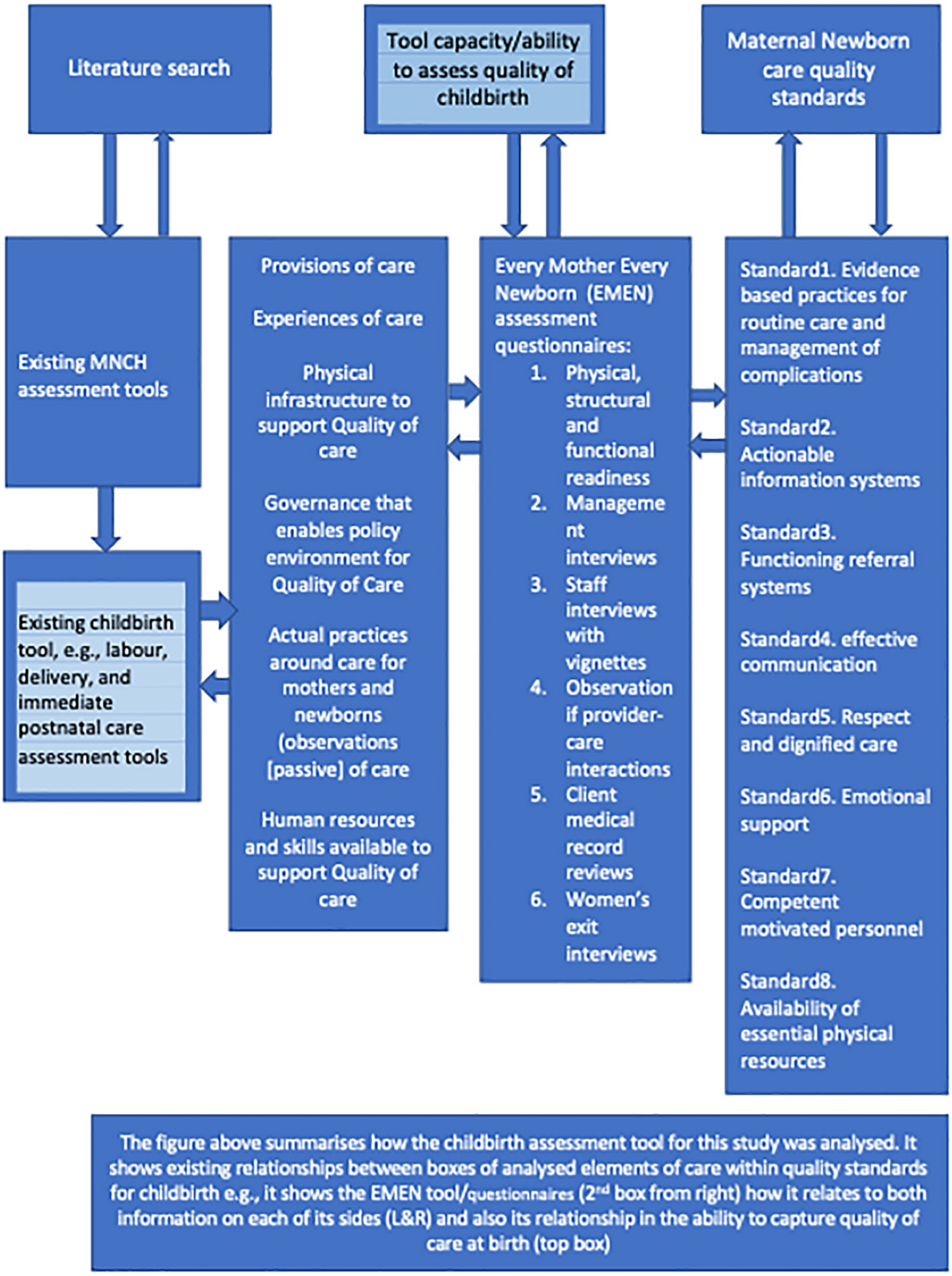

FIGURE 2
Conceptual model for analysis of childbirth healthcare assessment tools: A comprehensive measure of care elements (inputs, process and output, and outcomes).

tests, providers' attitudes, hygiene, and payment of legal and illegal fees.

This study only carried out the pre-assessment and documentation of the capacity of six EMEN tools to capture the WHO/UNICEF/UNFPA quality standards prior to data collection. The actual administration of the EMEN tools and its biases is reported elsewhere.

Adaptation and familiarisation of the study tools and relevance to other studies

The Donabedian and WHO/UNICEF frameworks for facility quality assessment, with three elements of inputs, process/outputs, and outcomes, were applied. Our study was built on other studies that used similar frameworks and tools (8–11, 13). This study used a similar scoring approach as the study by Brizuela et al. (11) who gauged the capacity of a variety of other tools to capture WHO measures. We expanded on these frameworks and created a conceptual model (**Figure 1**) on how we analysed and gauged the EMEN childbirth assessment tool against the WHO/UNICEF/UNFPA quality standards. Also, **Table 1** shows a short version of the WHO/UNICEF/UNPFA and EMEN quality measures that were assessable by using the EMEN tool.

Data analysis

All questions in each assessment tool were considered and matched against the WHO/UNICEF/UNFPA quality improvement standards for maternal and newborn care (5). We conducted descriptive data analysis summaries of all eight quality standards, 31 quality statements, and 352 quality measures. The descriptive analysis was carried out by summarising results into figures and tables. Our analysis included cross-matching questions from the tools with each quality measure within the quality statement under each quality standard (**Supplementary Appendix A** pp. 1–284).

Our scoring system was similar to that of Brizuela et al. (11). A question/wording from any tool that matched a quality measure was regarded as a match against a WHO quality measure within a particular quality statement (**Supplementary material**, pp. 1–284). A score of 1 was allocated for a quality measure matching a question. A quality measure was considered a match if one question and wording from the tool fulfilled one of the subcomponents of the quality measure. For instance, quality measure 1.1b:output/process 1.1b.3: "the proportion of all newborns who received all four elements of essential newborn care: immediate and thorough drying, immediate skin to skin contact, delayed cord clamping and initiation of breastfeeding in the first hour" can be matched by a question in the tool asking if the baby was exposed to skin-to-skin contact with the mother immediately after birth (5, 7). In addition, a single question and wording can match with more than one quality measure. For instance, a tool with a question regarding the availability of injectable antibiotics or was the woman/baby given antibiotics can be matched with a quality measure (QM) stating "the health facility has supplies of oral and injectable first-and-second-line antibiotics are available in sufficient quantities at all times for the expected case load" (QM1.7a: input1.7a.1), prophylactic antibiotics (QM1.6a. outcome1.6a.1), and also "appropriate antibiotic therapy" (QM1.8. output/process 1.8.2). Meanwhile, it can also match with the "availability of essential lifesaving medicines in the past three months" (QM8.3 output/process 8.3.1).

Ethical considerations

No human participants were involved in this study as the focus is on assessing the capacity of the EMEN tools to measure WHO/UNICEF/UNFPA quality improvement standards.

Results

The study results outlining the levels of strengths for the six EMEN tool/questionnaires is summarised in various tables and figures. For example, **Supplementary Figure 1** presents a summary of assessed WHO/UNICEF/UNFPA quality-of-care standards, statements, and measures. **Figure 1** depicts a conceptual model of how the analysis to determine the ability of the EMEN tool in capturing the WHO/UNICEF/UNFPA standards was conducted. **Supplementary Table 4** depicts key findings of this study by showing the performance of the EMEN tool against each of the WHO/UNICEF/UNFPA quality standards and statements. **Supplementary Table 4** also shows which tool was able to completely, partially, and not assess one or all quality measures. **Figures 2**, **3** extend the description of results in **Supplementary Table 4** to show the fulfilment of the quality standards and statements by the EMEN tool, respectively.

Summary coverage of WHO/UNICEF/UNFPA standards by the Every Mother Every Newborn tool

All the tools were able to fully assess (e.g., score 100%) two (2) or more quality statements. The management interview (F2:MI) fully assessed eight of the 31 quality statements (1.5, 1.6b, 2.1–2.2, 3.2, 5.1–5.2, and 7.3). The client medical record review (F5:CMRR) fully assessed seven of the 31 quality statements (1.2, 1.3, 1.4, 1.5, 1.7a, 1.7b, and 3.1). The physical

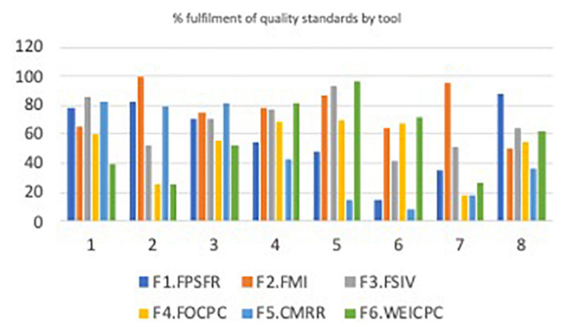

FIGURE 3
Fulfilment of the quality standards by tool.

structural readiness (F1:PSFR) tool was able to fully assess six of the 31 quality statements (1.2, 1.5, 1.8, 2.2, 8.2, and 8.3). Meanwhile, the staff interview with the vignette form (F3:SIV) fully assessed five of the 31 quality statements (1.6b, 1.7a, 1.7b, 5.1, and 5.2). Our analysis shows that structural, management, staff, and observation tools partially measured all 31 statements by assessing 66, 72, 74, and 55% of the 352 quality measures, respectively. However, the record review and women's exit interview tools partially measured 29 of the 31 quality statements by capturing 55 and 50% of the quality measures, respectively.

Completeness of quality measures coverages by Every Mother Every Newborn tool

Figure 3 shows how well each of the tools assessed each of the eight standards. While **Figure 4** displays how well each tool was able to assess the 31 quality statements; nine (3%) of the 352 quality measures (**Supplementary material**, pp. 284) were not assessed by any tool. Further analysis of the quality measures not assessed shows that 56% (five of nine) of the measures were within the experience of the care domain. Of the nine measures, three were related to evidence-based management (standard), two to effective communication, three to emotional support, and one to human resources (standard 7). All the EMEN tools were able to at least partially assess all eight quality standards, although women's exit interview and record review tools did not assess any measures for quality statements 1.5, 1.7b, 5.2, and 6.1 in standards 1, 5, and 6.

Overall, the tools were most comprehensive in assessing all the three components of care. For example, 100% (164 of 164) of input, 94% (103 of 110) of output/process, and 97% (76 of 78) of outcome measures (**Supplementary material**, pp. 1–284).

Although, all the tools assessed partially the eight standards. Our analysis shows that structural readiness, management, staff, and record review tools are strong (average 77%) in assessing evidence-based care, actionable information systems, and functioning referral systems (provisions of care). Effective communication, respect and dignity, and emotional support (experience of care domain) measures were highly assessable by management, observation, and exit interview tools at 76% average. At 65% average, management and staff interview tools were strong in capturing human and physical resources, whereas structural readiness captured 88% of physical resources.

Discussion

This is the first study to assess and compare the capacity of the EMEN childbirth assessment tool to measure WHO/UNICEF/UNFPA quality improvement standards. Thus, our results contribute to providing evidence of the UNICEF EMEN assessment tools for assessing current global standards of quality care at birth. Our results show that the EMEN assessment tools have the capacity to assess across the WHO/UNICEF/UNFPA quality improvement standards for maternal and newborn care at birth. The EMEN tools were able to broadly capture the three provisions of care, three experiences of care, and the two cross-cutting quality standards. This result supports comments from a study (8) on EMEN tools' strengths in capturing widely maternal–newborn quality improvement standards. In this study, the EMEN tools demonstrated a strong ability by assessing 97% (343 of 352) of the quality measures.

These results show the high capacity of EMEN tools in capturing the eight quality standard measures when compared to 274 measures included in the Brizuela et al. study (11). Our analysed measures were more because we included outcome measures, which were excluded in Brizuela et al. (11). When comparing the proportion of the 274 measures (inputs and outputs) covered in this study to Brizuela et al.'s study (11), we noted that very high percentage of measures were assessable (97.4%) by the EMEN tool. Of the total measures included in our analysis, only 3% measures were not measured by any EMEN tool when compared to 25% of the same measures not assessable in Brizuela et al.'s (12) study, which compared five existing tools separately (Demographic and Health Surveys programme Service Provision Assessment (SPA), the WHO Service Availability and Readiness Assessment, the Averting Maternal Death and Disability programme Needs Assessment of Emergency Obstetric and Newborn Care, and the World Bank's Service Delivery Indicator (SDI) and Impact Evaluation Toolkit).

Our results suggest that the EMEN tool has a strong ability to assess all three components of care. The completeness of the available measurement was high across the standards. We noted the highest captured measures for standard 2 information systems, standard 3 referral resources, standard 4 effective communication, standard 7 human resources, and

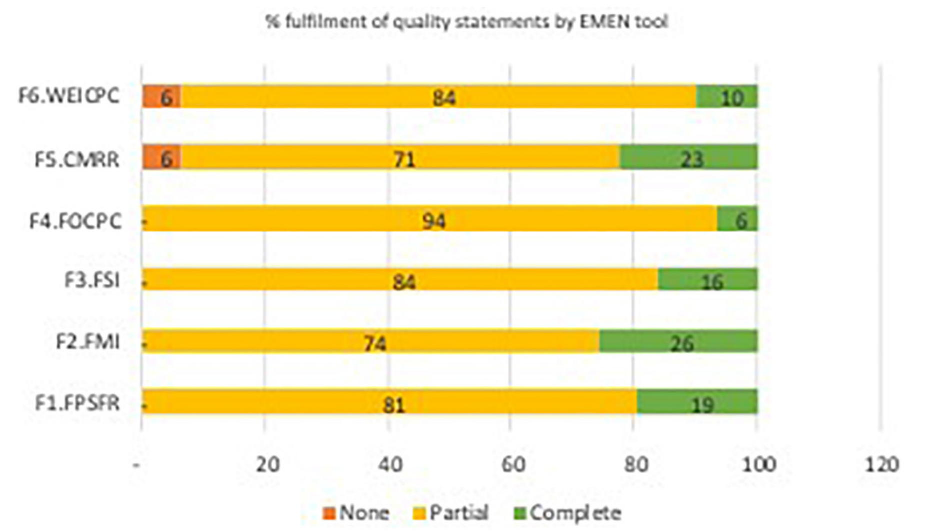

FIGURE 4
Fulfilment of quality statements by tool.

standard 8 physical resources. The high completeness for referral systems, physical resources, and standards 3 and 8, respectively, were consistent with the results of Brizuela et al. (11), which focussed primarily on tools that also assess systems and physical resources.

Our analysis also shows the very strong ability of the EMEN tool to capture experiences of the care domain or women's voices on how they perceived care, whereas previous tools had limited capacity to assess the experience of care within the WHO/UNICEF/UNFPA maternal and newborn quality standards. Capturing women's voices about their perception of care is crucial for improved healthcare (5, 12). Our analysis shows that women's exit interviews demonstrated the highest capacity in documenting women's reports of their experiences of care. Previous studies call to harmonise existing tools to include women's voices and capture outcome measures (11–13), which are addressed in the EMEN tool as demonstrated by this study. Yet, there is room for improvement as four of the nine measures not assessed by any tool are from experiences of care.

What is also new in this study is that we included an analysis of outcome measures in addition to the inputs and process measures commonly included in other studies (11, 12). The strength of the EMEN tool can be due to the inclusion of detailed input, output/process, and outcome items in their checklists/questionnaires. This is likely due to the EMEN tool being developed by pulling together best interventions of WHO SARA and those used in vigorous research settings (8). It is therefore not surprising that the EMEN tool's strengths in assessing the eight standards are high and address key weakness from widely available tools (11–13). We however encourage more researchers to implement the EMEN tool and document lessons, strengths, and weaknesses to strengthen the evidence on the ability of the tool.

However, we do note that the EMEN tool is long with pages ranging from 113 (for management and exit interviews) to 197 for the record review. At this stage, we cannot make any recommendations as to whether to shorten and or maintain them. What we can say is that the long and detailed questionnaires cover comprehensively the inputs, outputs, and outcomes and align with most measures across the eight standards. However, there are duplications across tools for some measures, but using any one tool alone does not adequately capture measures across the entire eight standards. There is a need to increase the implementation of the tools to document substantive experience in their usage to inform future recommendations.

Limitations

Our limitations are similar to the two (2) peer-reviewed published studies (11, 12), which used similar methods. The process of matching or deciding whether a question/item in the tool matched a quality measure within the WHO/UNICEF/UNFPA quality standards can be considered a limitation. Also, we only assessed the EMEN tool which does not assess beyond the childbirth or early newborn period.

Conclusion

The results of this study can benefit and contribute to future revisions of EMEN assessment tools and

WHO/UNICEF/UNFPA quality improvement standards. We call on academia, researchers, programmes, and policymakers to use EMEN tools to assess and determine quality care at birth. More use of the EMEN tools will ensure documentation of gaps, strengths, and opportunities toward maternal and newborn improved birth outcomes.

Although the EMEN tools widely assessed measures across the WHO/UNICEF/UNFPA standards, our analysis clearly shows that six EMEN questionnaires are intertwined and complement each other. Thus, the use of the full suite of tools, instead of single use is recommended, as no single questionnaire is comprehensive enough to capture all the measures.

The EMEN tools have demonstrated good capacity in capturing or determining quality healthcare provided at birth. As determining the quality of care at birth is crucial in informing strategic interventions at birth toward improved birth outcomes for women and newborns. Our results noted that other existing tools tended to emphasise input measures and were inadequate in assessing the experience of care. The need for consensus and harmonised key indicators from the WHO/UNICEF/UNFPA standards into a unified tool cannot be overstated.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The Ethical Review Board of the national-level Ministry of Health and Social Services (MoHSS), Namibia (Ref: 17/3/3) and the Research Ethics Committee of the University of the Western Cape (Ref: BM17/10/4) gave approval to carry out the study in Namibia. This study did not involve human participants.

Author contributions

GS led data collection and data analysis, and linkage with ministry and local stakeholders. TM and DJ were co-investigators and supervisors for the research. All authors participated in the conceptualisation of the study and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.959482/full#supplementary-material

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Factors influencing survival and short-term outcomes of very low birth weight infants in a tertiary hospital in Johannesburg

Kristin Ingemyr[1]*, Anders Elfvin[1,2], Elisabet Hentz[1,2], Robin T. Saggers[3,4] and Daynia E. Ballot[4]

[1]Department of Paediatrics, Institute of Clinical Sciences, University of Gothenburg, Sahlgrenska Academy, Gothenburg, Sweden, [2]Region Västra Götaland, Department of Paediatrics, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa, [4]School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

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EDITED BY
Susan Coffin,
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United States

REVIEWED BY
Lizelle Van Wyk,
Tygerberg Hospital, South Africa
Lloyd Tooke,
University of Cape Town, South Africa

*CORRESPONDENCE
Kristin Ingemyr
kristin.ingemyr@gmail.com

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Background: The neonatal mortality rate in South Africa is lower than the global average, but still approximately five times higher than some European and Scandinavian countries. Prematurity, and its complications, is the main cause (35%) of neonatal deaths.

Objective: To review the maternal, delivery period and infant characteristics in relation to mortality in very low birth weight (VLBW) infants at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods: This was a retrospective descriptive study of VLBW infants admitted to CMJAH between 1 January 2017 and 31 December 2018. All infants with a birth weight between 500 to ≤1,500 grams were included. The characteristics and survival of these infants were described using univariate analysis.

Results: Overall survival was 66.5%. Provision of antenatal steroids, antenatal care, Cesarean section, female sex, resuscitation at birth, and 5-min Apgar score more than five was related with better survival to discharge. Among respiratory diagnoses, 82.8% were diagnosed with RDS, 70.8% received surfactant therapy and 90.7% received non-invasive respiratory support after resuscitation. At discharge, 59.5% of the mothers were breastfeeding and 30.8% spent time in kangaroo mother care.

Conclusion: The two-thirds survival rate of VLBW infants is similar to those in other developing countries but still remains lower than developed countries. This may be improved with better antenatal care attendance, coverage of antenatal steroids, temperature control after birth, improving infection prevention and control practices, breastfeeding rates and kangaroo mother care. The survival rate was lowest amongst extremely low birth weight (ELBW) infants.

KEYWORDS

survival, short-term outcomes, infant, prematurity, neonatal mortality, very low birth weight (VLBW), premature neonate, low- and lower-middle-income countries

Introduction

In South Africa, the under-5 mortality rate in 2017 was 37.1 per 1,000 live births (1). South Africa and the rest of Sub-Saharan Africa failed to achieve the fourth Millennium Development Goal from the United Nations of a two-thirds reduction in the under-5 mortality rate (2). This is largely due to the relatively slow decline in the neonatal mortality rate over the last two decades (3).

During the neonatal period the mortality was 10.7 per 1,000 live births (4). While this is lower than the global average during the same time period (18.0 per 1,000 live births), it is higher than rates found in developed countries, such as Japan (0.9 per 1,000 live births), and approximately five times higher than some European and Scandinavian countries (4).

Prematurity, and its complications, is the main cause (35%) of neonatal deaths according to estimates developed by the United Nations Inter-agency Group for Child Mortality Estimation in their report from 2019. The second and third largest reasons contributing to neonatal mortality are intrapartum-related complications (24%) and sepsis (15%) (5). According to a review from The Gambia, factors which contribute to neonatal mortality include lack of antenatal care, birth weight <1,500 grams, hypothermia after birth and delivery outside teaching hospital (6).

The complications of preterm birth are many, due to immaturity of multiple organ systems (7). Some of these are intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), and retinopathy of prematurity (ROP).

This study aimed to review the maternal, delivery period and infant characteristics in relation to mortality in VLBW infants at the CMJAH. The acquired information will be useful to improve the neonatal care and neonatal survival at CMJAH.

Materials and methods

Study design

This was a retrospective observational study of VLBW infants admitted to CMJAH. All infants with birth weight between 500 to ≤1,500 grams, born between 1 January 2017 and 31 December 2018 and admitted to the neonatal unit at CMJAH were included. Infants with incomplete data for birth weight, place of birth and date of outcome were excluded.

Setting

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a large tertiary referral hospital within the public hospital framework in South Africa. South Africa is considered a developing country and has limited health resources and high patient numbers. In this setting it is not possible to provide full support to every very low birth weight (VLBW) infant due to necessity of rationing care. Therefore, intermittent positive pressure ventilation (IPPV) after the resuscitation period is not routinely provided to infants who weigh <800 grams in this institution based on anticipated poor outcome, prolonged ventilation, and high use of resources.

At CMJAH there is a quality improvement project called PRINCE—the Project to Improve Neonatal Care—with the purpose to develop targeted interventions to improve the neonatal care and clinical outcome of infants at CMJAH. PRINCE has been accredited as a research programme within the Faculty of Health Science at the University of Witwatersrand.

Database and data collection

Data was managed using the Research Electronic Data Capture (REDCap) computer database, hosted by the University of Witwatersrand (8, 9). The REDCap computer database at CMJAH started in 2013 and information is collected at discharge. Medical staff collect the data from the patient records, before it is entered on to a computer summary form and then the database itself, with multiple checks and verification. Records contain information such as demographics, clinical characteristics, hospital course, and outcome at discharge.

Variables

Variables were selected from amongst those available from the database and considered as of possible importance for preterm delivery and the short-term outcome. The studied maternal characteristics were: maternal age, multiple gestation, parity, maternal HIV status, maternal syphilis, antenatal care, antenatal steroids. The studied characteristics for the delivery period were: place of birth (inborn or outborn), mode of delivery (vaginal or Cesarean section), 5-min Apgar score. The studied infant characteristics were: gestational age, birth weight, head circumference at birth, sex, birth HIV PCR, initial resuscitation in the delivery room, and hypothermia.

Factors related to hospital stay and neonatal complications that were studied included age on admission, age at outcome, respiratory diagnosis (RDS, congenital pneumonia, pulmonary

Abbreviations: BPD, Bronchopulmonary dysplasia; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; ELBW, Extremely low birth weight; IPPV, Intermittent positive pressure ventilation; IVH, Intraventricular hemorrhage; KMC, Kangaroo Mother Care; NCPAP, Nasal continuous positive airway pressure; NEC, Necrotizing enterocolitis; NNJ, Neonatal jaundice; PDA, Patent ductus arteriosus; PRINCE, Project to Improve Neonatal Care; RDS, Respiratory distress syndrome; REDCap, Research Electronic Data Capture; ROP, Retinopathy of prematurity; VLBW, Very low birth weight.

hemorrhage, pneumothorax), surfactant therapy at any time, respiratory support after initial resuscitation (non-invasive or invasive), any respiratory support after 36 weeks, steroids for BPD, screening for ROP, ROP stage 3 or 4, IVH grade 3 or 4, PDA, NEC grade 2 or 3, early-onset sepsis, late-onset sepsis, surgery for NEC, other surgery, blood transfusion, neonatal jaundice requiring phototherapy, congenital anomalies, Kangaroo Mother Care (KMC), and breastfed at discharge.

Definitions

VLBW infants were defined as birth weight ≤1,500 grams. Extremely low birth weight (ELBW) infants were defined as birth weight ≤1,000. Short-term outcome was defined as death or survival to discharge. For diseases, standard definitions as per the Vermont Oxford Network were used (10). Sepsis was defined as blood-culture proven isolation of a pathogenic organism. Early-onset sepsis was defined as onset within 72 h of life and late-onset sepsis after 72 h of life. Patent ductus arteriosus was diagnosed with echocardiography (performed by cardiologists) after clinical suspicion.

Attendance at antenatal care constituted at least one antenatal visit during pregnancy. Place of birth was divided into inborn (infants born within CMJAH) and outborn, including infants born before arrival, at midwife obstetric units or born at other hospitals and referred to CMJAH. Mode of delivery was divided into vaginal delivery (including vertex and breech presentation) and Cesarean section (including elective and emergency cases). Gestational age at birth was decided from the best obstetric estimation available (firstly maternal dates, secondly early ultrasound or thirdly late ultrasound). If none of the above was available, gestational age was estimated using the Ballard Score (11).

Hypothermia was defined as body temperature <36.5 degrees Celsius, measured within 1 h of admission to the neonatal unit. Respiratory support after initial resuscitation was divided into non-invasive and invasive ventilation. Non-invasive respiratory support included nasal-prong oxygen, nasal continuous positive airway pressure (NCPAP) and high flow nasal cannula oxygen, whereas invasive respiratory support included conventional mechanical ventilation and high frequency ventilation. Similarly, respiratory support at 36 weeks was used to determine severity of BPD, based on the level of support of the earlier mentioned alternatives. During the study period, there was a weight cut off for invasive ventilation at 800 grams and for NCPAP at 750 grams. ELBW who did not qualify for invasive or non-invasive ventilation due to their birth weight, were offered surfactant then placed on nasal prong oxygen.

Mothers were screened for HIV at antenatal care visits and again at delivery. Babies born to HIV-positive mothers had an HIV PCR test performed at birth and were put on to HIV prophylaxis dependent on their level of exposure risk. The requirements for surfactant therapy were preterm infants who were hemodynamically stable, with changes suggestive of RDS on chest X-ray, who had respiratory distress and who required fraction of inspired oxygen ≥40% oxygen to keep oxygen saturations >89%. Cranial ultrasound was performed within the first seven days of life and repeated at 10–14 days of life and then again prior to discharge.

All babies with a birth weight ≤1,500 grams or gestational age at birth below 32 weeks, were screened for ROP, at 4 to 6 weeks chronological age. Breastfed on discharge included breastmilk only, fortified breastmilk or breastmilk and formula together. KMC included both intermittent and continuous. KMC was introduced once a baby weighed over 1,200 grams, tolerated full enteral feeds, had an adequate weight gain (>15 g/kg/day), was off supplemental oxygen and could maintain temperature and glucose levels. Survival as outcome included discharged to home or transferred to another hospital. Babies were discharged home once they had achieved a weight of 1,600 grams, established enteral feds, were off supplemental oxygen, maintained temperature and glucose levels.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25. Frequencies and percentages were used to describe categorical variables. Continuous variables were described using mean and standard deviation if they were normally distributed, and median and interquartile ranges (IQR) if they were skewed. Univariate analysis was performed to determine significant associations of various factors with survival at discharge. Unpaired *t*-tests were used comparing normally distributed continuous variables and Mann-Whitney *U* tests for skewed distribution. Chi-Square tests were used to compare categorical variables. A *p*-value of <0.05 was considered significant. Only valid cases were analyzed for each variable (i.e., cases with missing data were excluded from the analysis). Thereafter a multiple logistic regression model with mortality as the binary outcome variable was performed. Variables that were (1) significantly associated with mortality in univariate analysis, (2) had a sufficient number of valid cases, (3) passed the assumption of linearity using Box-Tidwell procedure, (4) were not transformed as part of the initial univariate analysis, and (5) were appropriate were included in the model.

Ethics

Ethical approval for the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number M190874). As this was a retrospective audit of an existing database, informed consent was waived. All methods were carried out in accordance with relevant guidelines and regulations.

Results

There were 946 VLBW infants admitted during the study period. Eight infants were excluded (seven infants weighed <500 grams at birth, one infant did not have a date of outcome recorded), 938 VLBW infants were included in the study. The overall survival rate was 66.5% (624/938). The mean birth weight was 1,093.6 grams (SD: ± 249.9), mean gestational age at birth was 28.9 weeks (SD: ± 2.8) and median age at outcome was 27.0 days (IQR: 38).

Maternal details and delivery period

The mean maternal age was 28.8 years (SD: ± 6.4) and 28.5% (222/780) were primiparous. There were 16.6% (152/913) multiple gestation. Risk factors with significant result for mortality related to antenatal care, labor and delivery are presented in Table 1.

Among the mothers 29.6% (275/929) were HIV positive and 1.7% (16/868) positive for syphilis. A total of 78.6% (737/938) infants were inborn. Temperature measured within 1 h of admission showed 60.8% (463/762) of the infants had hypothermia. These results were not significant in relation to mortality.

Infant details

The birthweight, gestational age and head circumference of survivors were significantly greater compared with the infants who died (see Table 2). The 5-min Apgar score of survivors was significantly higher than for the non-survivors (see Table 2). Birth HIV PCR was done in 93.6% (249/266) of cases where the mother was HIV positive and of these 2.8% (7/249) infants were positive for HIV.

Survival by birth weight category is shown in Figure 1. The survival of infants with a birthweight from 1,000 to <1,500 grams was 82.2% (514/625) and was significantly greater ($p <$ 0.001) compared to the group of extremely low birth weight infants (ELBW) at 35.1% (110/313).

Hospital stay and neonatal period

Treatments and complications during the neonatal period and hospital stay with statistically significant result for mortality are shown in Table 3.

There were 90.7% (851/938) of infants who received non-invasive respiratory support after initial resuscitation. Under respiratory diagnosis, 82.8% (777/895) of the infants were diagnosed with RDS and 0.5% (5/935) babies with congenital pneumonia. These results were not significant in relation to mortality. Other respiratory diagnoses which were significant in relation to mortality are included in Table 3.

PDA was reported in 9.2% (85/927) of cases. Among the infants with sepsis there were 4.5% (42/902) with early-onset sepsis and 32% (298/930) with late-onset sepsis. 43.2% (399/924) of the infants received blood transfusion. These results were not significant in relation to mortality.

Screening for ROP occurred in 30.1% (273/906) of the infants and among these 2.9% (8/273) of infants had ROP stage 3 or 4. Breastfeeding at discharge occurred in 59.5% (322/541) of the infants and 30.8% (283/920) spent time in KMC.

There were 22 significant variables on univariate analysis. Six variables (steroids for BPD, pulmonary hemorrhage, pneumothorax, congenital anomalies, IVH grade 3 or 4, and other surgery) were excluded as there were not enough valid cases for both outcomes to include in the logistic regression model. The three continuous variables (birthweight, head circumference, and gestational age) all failed the Box-Tidwell procedure for linearity and were thus excluded from the model. 5-min Apgar score was presented as both an ordinal variable and a transformed categorical variable and was excluded as neither were appropriate for this model. NEC surgery was excluded as it is dependent on NEC 2 or 3, to avoid circular reasoning.

Of the 10 predictor variables included (sex, antenatal care, antenatal steroids, mode of delivery, resuscitation at birth, invasive respiratory support after initial resuscitation, respiratory support after 36 weeks, surfactant at any time, NEC 2 or 3, and neonatal jaundice), seven were statistically significant as shown in Table 4. The logistic regression model explained 44.0% of the variance in outcome and correctly classified 79.5% of cases.

Discussion

This retrospective review showed an overall two-thirds survival of VLBW infants. This is decreased when compared with the results from previous studies at the same unit where the overall survival of VLBW infants in 2006/2007 was 70.5% and in 2013 was 73.4% (12, 13). These survival rates are similar to those found in other parts of South Africa namely the Eastern Cape province (68.0%), but lower than reported in the Western Cape (81.7%) and in Limpopo (77.4%) (14–16). Further afield, the survival rate in this study compares to other developing countries (like India and Iran) (17, 18) but still remains lower than developed countries (19).

The survival of ELBW in this study is comparable to that found in the 2006/2007 study (13), but lower

TABLE 1 Obstetric risk factors, infant characteristics and prediction of mortality.

Risk factor (valid cases)		Total *n*	Survived *n* (%)	Died *n* (%)	*P* value	Odds ratio	95% CI of OR
Sex (938)	Male	426	260 (61.0)	166 (39.0)	0.001	1.57	1.20–2.06
	Female	512	364 (71.1)	148 (28.9)			
Antenatal care (869)	Yes	687	486 (70.7)	201 (29.3)	<0.001	0.41	0.30–0.58
	No	182	91 (50.0)	91 (50.0)			
Antenatal corticosteroids (812)	Yes	392	276 (70.4)	116 (29.6)	0.021	0.70	0.53–0.94
	No	420	263 (62.6)	157 (37.4)			
Mode of delivery (894)	Vaginal	401	229 (57.1)	172 (42.9)	<0.001	0.46	0.34–0.61
	Cesarean section	493	367 (74.4)	126 (25.6)			
Resuscitation at birth (823)	Yes	427	230 (53.9)	197 (46.1)	<0.001	3.38	2.48–4.62
	No	396	316 (79.8)	80 (20.2)			
5-min Apgar Score (810)	≤ 5	115	68 (59.1)	47 (40.9)	0.042	1.52	1.02–2.28
	> 5	695	478 (68.8)	217 (31.2)			

Valid cases, those with no missing data.
Percentages reported for rows.
CI, Confidence interval.

TABLE 2 Infant characteristics comparing survivors to non-survivors.

Category	Survivors $n = 624$	Non-survivors $n = 314$	*P*-value
Birthweight, g (mean, SD)	1,186.4 (197.8)	909.1 (240.4)	<0.001
Gestational age at birth, weeks (mean, SD)	29.7 (2.5)	27.2 (2.6)	<0.001
Head circumference, cm (mean, SD)	27.8 (2, 2)	25.5 (2.7)	<0.001
5-min Apgar score, (median, IQR)	9 (1)	7 (4)	<0.001

IQR, interquartile range, SD, Standard deviation.

than the more recent study from the same unit in 2013 (12). Sadly, our results amount to only about half the survival rate that was achieved in a study from the Western Cape (20).

A possible reason for the lower survival rate could be the increase in late-onset sepsis in this study. In 2013, 19% of the VLBW infants at CMJAH had late-onset sepsis, whereas in this study there was an incidence of 32% (12). This may be a consequence of over-crowding or poor adherence to infection prevention and control practices.

In this study 78.6% of the infants were inborn which could be compared with 81.5% in 2006/2007 and 84.3% in 2013 (12, 13). The result was not significant in relation to mortality, which it was in 2006/2007 and 2013. A study in Cape Town, South Africa, found that being inborn was significantly associated with improved survival and decreased morbidity: mothers of inborn infants were more likely to receive antenatal care and antenatal steroids, inborn infants required less ventilatory support, surfactant administration and developed less late-onset sepsis, IVH and BPD (21).

When it comes to antenatal steroids, the coverage in this study had improved slightly (from 39.1 to 48%) compared to 2013 (12). However, this remains poor compared to other South African studies (15, 16, 22). Despite this improvement the goal should be even higher since antenatal steroids have an effect on RDS (hence the amount of respiratory support required for patients), as well as the rates of NEC and IVH (23). Lategan et al. found that exposure to any antenatal steroids was associated with a nearly three-quarter reduction in mortality in their cohort of preterm infants ≤1,800 (15). Concerted efforts need to be made to further improve the coverage of antenatal steroids.

Despite the modest improvement in antenatal steroid coverage, the rates of NEC (12.3% vs. 7.3%) and IVH (11.5% vs. 7.9%) in this study has increased compared to 2013 (12). The increased rate of NEC may be due to the increased rate of late-onset sepsis as mentioned above, and vice versa. The increased rate of IVH may be due to increased screening.

When measuring body temperature within 1 h of admission, 60.8% of the infants had hypothermia (skin temperature <36.5 degrees Celsius). Earlier studies done at the same department had not stated their definition of hypothermia, so no comparison

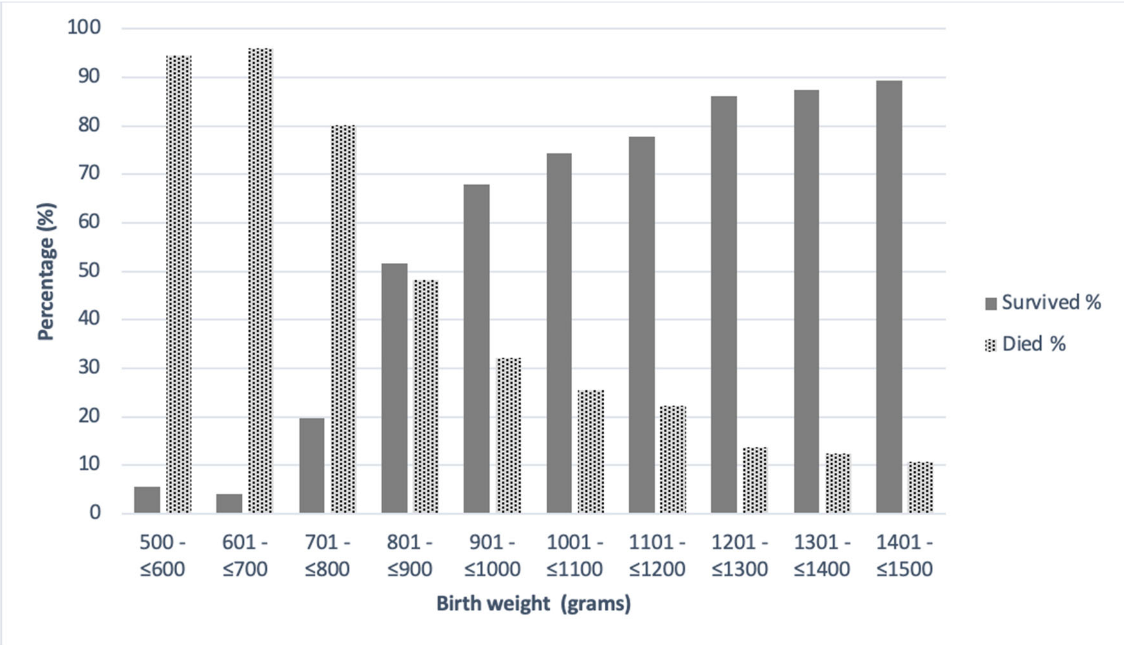

FIGURE 1
Survival by weight category. Survival of very low birth weight infants by birth weight category.

could be made. However, this is interpreted as a large number and needs to be improved. Hypothermia increases morbidity (of which RDS is one) and mortality (22). This may have contributed to the large number of infants diagnosed with RDS in this study. Simple, cost-effective measures can be employed to prevent hypothermia, such as increasing awareness of its dangers, regular body temperature monitoring, warmed delivery rooms, providing infants with caps and plastic bags to limit heat loss, and making use or servo-controlled incubators and radiant warmers (which are already in use).

Several diseases showed significant association with mortality, such as pulmonary hemorrhage, congenital anomalies, IVH and NEC. This indicates the severity of these conditions. In addition, surgery for NEC and other surgery were also significantly associated with mortality, although that may be related to the severity of the condition rather than the surgery itself. Predictably, infants with congenital anomalies had higher mortality. It is unit policy not to offer invasive ventilation to infants with congenital anomalies with poor prognosis (e.g., Trisomy 13 and 18).

Taking logistic regression into consideration, receiving any respiratory support during initial resuscitation, surfactant at any time, as well as invasive ventilation after initial resuscitation was associated with higher odds of mortality. The high use of surfactant replacement therapy found in this study is concerning. During the study period, delays were frequently encountered when instituting NCPAP due to equipment shortages. This may have caused infants to deteriorate sufficiently to necessitate surfactant replacement therapy. Efforts have been made to address the delays and improve the use of NCPAP, thereby decreasing the use of surfactant therapy.

Several improvements can be made in the neonatal care prior to discharge. For instance, screening for ROP is supposed to be done on all VLBW infants and was only performed in one third of them prior to discharge in this study. This is still an improvement compared to 2006/2007 when 18.3% of the infants were screened for ROP prior discharge (13). Since the infants are discharged at 1,600 grams, the appropriate time for screening may be after discharge—infants were referred for ophthalmological screening as an outpatient.

In recent years, efforts have been made to increase the number of breastfed infants at discharge, considering the well-documented benefits of breastfeeding and its affordability. To this end, several lactation consultants have been employed. As a result, the number of breastfed infants at discharge has nearly doubled from 2013 (30.5%) to the current rate in this study, which is commendable (12).

On the other hand, KMC has decreased in this study compared with 2006/2007 (30.8% vs. 44.5%) (13). The limitations of KMC in this unit is the availability of mothers—many are single parent households and have to be at home looking after other children. It is important to improve these numbers again since KMC has shown positive results when it comes to better weight gain, earlier hospital discharge and higher exclusive breastfeeding rates in VLBW infants (24, 25).

TABLE 3 Risk factors for mortality related to disease and treatment among studied infants.

Risk factor (Valid cases)		Total n	Survived n (%)	Died n (%)	P value	Odds ratio	95% CI of OR
Invasive respiratory support after initial resuscitation (938)	Yes	245	115 (46.9)	130 (53.1)	<0.001	3.13	2.31–4.23
	No	693	509 (73.4)	184 (26.6)			
Respiratory support after 36 weeks (938)	Yes	148	126 (85.1)	22 (14.9)	<0.001	0.30	0.19–0.48
	No	790	498 (63.0)	292 (37.0)			
Surfactant therapy at any time (894)	Yes	633	392 (61.9)	241 (38.1)	<0.001	2.15	1.54–3.00
	No	261	203 (77.8)	58 (22.2)			
Steroids for BPD (823)	Yes	171	159 (93.0)	12 (7.0)	<0.001	0.14	0.07–0.25
	No	652	419 (64.3)	233 (35.7)			
Pulmonary hemorrhage (936)	Yes	16	2 (12.5)	14 (87.5)	<0.001	14.54	3.28–64.83
	No	920	621 (67.5)	299 (32.5)			
Pneumothorax (924)	Yes	22	9 (40.9)	13 (59.1)	0.012	2.99	1.26–7.07
	No	902	608 (67.4)	294 (32.6)			
IVH grade 3 or 4 (610)	Yes	70	19 (27.1)	51 (72.9)	<0.001	11.81	6.68–20.88
	No	540	440 (81.5)	100 (18.5)			
NEC grade 2 or 3 (932)	Yes	115	65 (56.5)	50 (43.5)	0.015	1.66	1.11–2.47
	No	817	558 (68.3)	259 (31.7)			
Surgery for NEC (908)	Yes	33	15 (45.5)	18 (54.5)	0.008	2.55	1.27–5.13
	No	875	595 (68.0)	280 (32.0)			
Other surgery (905)	Yes	30	15 (50.0)	15 (50.0)	0.049	2.10	1.01-4.36
	No	875	593 (67.8)	282 (32.2)			
Neonatal jaundice requiring phototherapy (919)	Yes	479	352 (73.5)	127 (26.5)	<0.001	0.53	0.40–0.70
	No	440	262 (59.5)	178 (40.5)			
Congenital anomalies (925)	Yes	24	8 (33.3)	16 (66.7)	0.001	4.17	1.77–9.86
	No	901	609 (67.6)	292 (32.4)			

Valid cases, those with no missing data.
Percentages are reported for rows.
CI, Confidence interval; BPD, Bronchopulmonary dysplasia; IVH, Intraventricular hemorrhage; NEC, Necrotizing enterocolitis.

TABLE 4 Multivariate logistic regression for factors associated with mortality in very low birth weight infants at Charlotte Maxeke Johannesburg Academic Hospital.

Category	OR	95% CI	P-value
Invasive ventilation	7.314	4.373–12.232	<0.001
Resus at birth	3.144	2.091–4.726	<0.001
Surfactant therapy	2.329	1.447–3.747	<0.001
Antenatal care	0.410	0.253–0.666	<0.001
Mode of delivery	0.311	0.202–0.480	<0.001
NNJ requiring phototherapy	0.291	0.194–0.438	<0.001
Respiratory support at 36 weeks	0.033	0.014–0.079	<0.001

CI, confidence interval; NEC, necrotizing enterocolitis; OR, odds ratio.

Limitations

We acknowledge several limitations to this study. This was a retrospective analysis of an existing database, so some information was missing. Additionally, certain data such as usage of parental nutrition and antibiotics usage, is not routinely collected in the database and were therefore not analyzed. Our study favored maternal dates and Ballard score to determine gestational age as access to early ultrasound is poor. The short-term outcome of survival to discharge included infants discharged home and to other hospitals. We did not look at categorizing the timing of when deaths took place which would be useful in identifying trends. Importantly, this is not a population-based study. This study was conducted in a referral hospital with access to the appropriate level of care, as per national guidelines.

Conclusion

This study showed a two thirds survival rate in VLBW infants, which is similar to those in other developing countries (like India and Iran) but still remain lower than developed countries. A large number of patients are placing a burden on a hospital with limited resources. The survival rate can be improved by increasing antenatal care attendance, coverage of antenatal steroids, improving temperature control to decrease the high rates of hypothermia, improving infection prevention and control practices, breastfeeding rates and the use of KMC. Improved screening for morbidities such as ROP and IVH should also be emphasized.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of the Witwatersrand Human Research Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

KI conceptualized and designed the study, collected data, carried out data analysis, drafted the initial manuscript, revised the manuscript, and approved the final manuscript. AE, EH, and RS participated in protocol development, supervised the study, reviewed and revised the manuscript, and approved the final manuscript. DB supervised the study, revised the manuscript, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Christian Victor Hulzebos,
University Medical Center Groningen,
Netherlands

REVIEWED BY
Mahendra Tri Sampurna,
Airlangga University, Indonesia
Kazumichi Fujioka,
Kobe University, Japan
Cinzia Auriti,
Bambino Gesù Children's Hospital
(IRCCS), Italy

*CORRESPONDENCE
Britt Nakstad
britt.nakstad@medisin.uio.no

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Ophthalmomyiasis in a preterm neonate resulting in blindness: A case report from Botswana

Britt Nakstad[1,2]*, Yeni Zandile[1], Kesiilwe Gaebolae[3], Francis Msume Banda[1], Tebo Dinotshe[1], Fizzah Imran[1] and Alemayehu Mekonnen Gezmu[1]

[1]Department of Paediatrics and Adolescent Health, University of Botswana, Gaborone, Botswana, [2]Division Paediatric Adolescent Medicine, Inst Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [3]Department of Ophthalmology, Princess Marina Hospital, Gaborone, Botswana

Myiasis is an infestation of human tissue by insect larvae. While rare, healthcare-associated myiasis has been reported from immobilized patients in resource-limited healthcare facilities in warm climates without adequate vector control measures. We describe a case of Ophthalmomyiasis in a hospitalized neonate in Botswana that resulted in vision loss. The neonate, who was initially hospitalized due to the complications of prematurity, received phototherapy for jaundice, and to avoid phototherapy-related retinopathy, the neonate's eyes were covered using cotton gauze and adhesive tapes that potentially damaged the skin as commercially available eye covering was not in stock. Therefore, eye covering was not changed and when the eye covering was removed almost 3 days after placement, insect larvae were noted in the patient's eyes and nose. Ophthalmologic evaluation revealed perforated corneal ulcer and uveal prolapse in the right eye resulting in complete blindness and corneal scarring of the left eye. The patient's clinical course was further complicated by an *Enterobacter* species bloodstream infection. This case highlights the importance of vector control as a major patient safety measure for neonatal units in warm climates. Flies had been observed in the room and mitigation measures included reducing fly populations through traps, screens, and removal of standing water and leftover food. Every mother and staff were sanitizing hands when entering the room and gowns were used. This case also reinforces the importance to conduct vigilant monitoring of patients, especially neonates with eyes covered during phototherapy.

KEYWORDS

preterm neonate, ophthalmomyiasis, blindness, jaundice, eye-covering during phototherpy

Introduction

Myiasis is an infestation of human tissue by larvae of a variety of fly species. Insect larvae (i.e., maggots) feed off and develop in the tissues of living organisms when adult flies lay eggs in or on the tissues. While rare, myiasis has been reported in adults living in tropical and subtropical regions, particularly as wound infestations in settings where flies are present and are able to contact openings and wounds (1, 2). Healthcare-associated myiasis is associated with insufficient supervision of immobilized patients in warm climates (3). Myiasis is even rare in neonates. Whereas most published cases in neonates describe community-acquired umbilical myiasis (4–10), neonatal ophthalmomyiasis has been scantily described (2, 11, 12). Other sites reported among neonates are ear (13), nasopharynx (14), oral (15), skin (16), and intestine (17). Powdered infant formula has also been noted to have been contaminated (18). A case of neonatal myiasis leading to *Enterobacter cloacae* sepsis was described in a premature neonate in Botswana (not reported), but to our knowledge, this is the first report of neonatal ophthalmomyiasis leading to blindness. This case report refers to a vulnerable neonate born 13 weeks before term with very low birth weight, needing intensive care and follow-up, and cared for in an intensive care unit that was understaffed, overcrowded, and equipment and reagents for measuring hyperbilirubinemia out of stock. This paved the way for improved guidelines outlining frequent (every 8 h) checks of eye coverings and implementation of vector control as an infection prevention measure. Although this unit is staffed by competent and caring healthcare personnel, this report reminds us that staff shortages can compromise the safety, especially in healthcare settings prone to insect infestation.

Case description

The parents of this patient provided written consent for the data collection and presentation of findings.

Medical history

In Botswana during the summer months, a male neonate was born to an HIV-negative and venereal research laboratory (VDRL) non-reactive mother at 27 weeks gestational age (GA). APGAR scores were 5/7/8 at first/fifth/10th minutes, respectively, and he required resuscitation by mask and bag ventilation at birth. He was given tetracycline eye ointment which is routinely given as prophylaxis against ophthalmia neonatorum as delivering mothers in Botswana are not screened for chlamydia and gonococcal infections. Vitamin K was given intramuscularly to prevent hemorrhagic disease. Due to persistent respiratory distress, the patient was admitted to the neonatal unit of a tertiary hospital, intubated, mechanically ventilated, and started on first-line antibiotics (ampicillin and gentamicin) as empiric treatment for suspected sepsis. Initial white blood cell counts were 11.87 × 10^9/L (26% neutrophils) and platelets 207 × 10^9/L. Infection biomarkers were not available, but the blood culture collected prior to empiric antibiotic administration grew *Enterobacter* sp. (un-speciated).

FIGURE 1
Insect larvae in the eyes and coming out of the nostrils.

The patient was noted to be clinically jaundiced age 30 h (serum total bilirubin was 184 mmol/L), secondary to suspected Rh isoimmunization, and was started on phototherapy (PT) and intravenous immunoglobulin. To prevent PT-associated retinopathy, the patient's eyes were covered using cotton gauze and adhesive tape because commercially available eye covering was not in stock.

On day-of-life (DOL) 2–4, the patient displayed signs of clinical deterioration: pulmonary hemorrhage (as evidenced by fresh blood in the endotracheal tube, treated with fresh frozen plasma, vitamin K, and adrenaline via the endotracheal tube), Grade 3 intraventricular hemorrhage, and acute kidney injury (urea 14.1 mmol/L and creatinine 89 mmol/L). Antibiotic coverage was broadened to piperacillin–tazobactam and amikacin.

Because the neonatal unit only had cotton gauze and adhesive tape for use as an eye covering, there was a fear to damage the skin if the adhesive tape was repeatedly removed during phototherapy. However, when the patient's serum bilirubin had declined to below phototherapy indication levels at DOL3, the eye covering was removed. There was now bilateral periorbital edema with erythema, the right eye being more affected than the left. Insect larvae of different sizes were identified in both eyes upon retracting the eyelids and some were even seen coming out of the nostrils. None were noted in from the mouth or auricular orifices (see **Figure 1**).

FIGURE 2
The right eye perforated corneal ulcer with uveal prolapse.

Insect larvae were immediately and carefully removed manually, followed by rinsing the eyes with sterile, normal saline. Chloramphenicol eye ointment was initially applied to both eyes. Upon ophthalmologist's review, it was discovered that the patient had a corneal ulcer in the left eye with injected and reddish conjunctival tissue, while deeper structures were difficult to explore due to a hazy cornea. There was periorbital swelling and the conjunctival and surrounding tissues were injected and inflamed. In the right eye, a perforated corneal ulcer with uveal prolapse was observed on the inferior aspect of the cornea (**Figure 2**). The left eye was lavaged two to three times daily with sterile saline to wash out pus. Topical tetracycline plus gentamicin eye ointment and ofloxacin eye drops were alternated 2 hourly. According to the ophthalmologist, evisceration of the right eye could be done once the baby was off the ventilator and become clinically stable.

On discharge, the corneal ulcer on the left eye had healed with a corneal scar. There was right eye phthisis bulbi (Grade I) with a symblepharon inferiorly. Evisceration was, therefore, deemed no longer necessary (**Figure 3**).

There were no signs of retinopathy of prematurity (ROP) screening on further ophthalmologic assessment of the left eye. The retina was fully vascularized up to the far periphery (Stage 0 ROP, Zone III). The patient was discharged to his local hospital on topical artificial tears four times a day on the right eye only, and to continue follow-up in ophthalmology clinic as an outpatient.

Discussion

We report a case of neonatal ophthalmomyiasis which was likely delayed in being diagnosed due to an eye covering *in situ* during phototherapy. This led to complete blindness

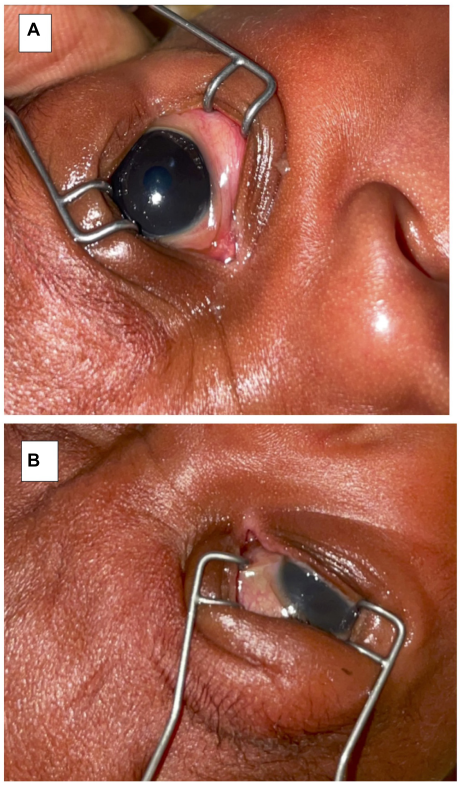

FIGURE 3
Upon discharge **(A)** left eye examination showing a corneal scar and **(B)** right eye showing phthisis bulbi and symblepharon.

in one eye, while the other eye healed well and resulted in a corneal scar only. This case emphasizes the vulnerabilities of hospitalized neonates in inpatient units that periodically experience insect infestations.

This case highlights the importance of vigilant monitoring of neonates as they are unable to mechanically remove flies or maggots from their faces, including eyes. Understaffed units may not be equipped to monitor patients with the frequency and thoroughness which is needed to detect such abnormalities. Sick and hospitalized neonates may be especially at risk and predisposed to insect infestation in covered eyes, wounds, and umbilical stumps if flies are in the room as they often are kept naked under a radiant warmer, for observation. Prematurity may also pose an increased risk of infection due to an immature immune system.

Treatment of myiasis consists of removal of the larvae and control of local and systemic infection, if any. In our case, any dead or decaying deep-seated larvae that could cause secondary infection or sepsis were removed manually, followed by daily lavage with sterile normal saline, local treatment with antimicrobial ointments, and continuous intravenous antibiotic treatment. Petroleum ointment or topical ivermectin solution may be an alternative medication to smoothly remove or kill larvae (19). Surgery was not necessary or indicated. The fact that this is the second case of *Enterobacter* sepsis following neonatal myiasis in this setting emphasizes the potential of flies and fly larvae to serve as transmission vehicles for bacterial infection (20).

This neonate was subjected to several hours of eye covering using cotton and tape which was the only available material. There was a fear to damage the skin if the adhesive tape was repeatedly removed during phototherapy. The skin and ocular area under the covering were not examined during phototherapy, not until treatment was stopped (**Figure 1**). According to the neonatal nursing staff, his eyes had been continuously covered and the tape removed intermittently to avoid traumatizing the skin in the face. The routine for eye covering in our unit has now been changed and procedures introduced to check the area under the eye covering two times daily when a neonate is under phototherapy.

Essential points and patient perspective

Neonatal myiasis is a risk in warm climates, particularly among neonates with covered eyes during phototherapy for neonatal jaundice, open wounds, or an exposed umbilical stump. Neonatal units must include vector control as a core patient safety strategy. Mitigation measures include reducing fly populations through traps, screens, and removal of standing water and food. Additionally, adequate staffing and access to non-adhesive eye coverings are essential for healthcare workers to complete frequent and thorough monitoring.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

BN drafted the manuscript with inputs and acceptance of the final version of the manuscript by all co-authors. All authors were involved in treatment and discussions related to the patient and accepted the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Andrew Steenhoff,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Mathilde Crone,
Leiden University Medical Center (LUMC), Netherlands
Suresh Munuswamy,
Public Health Foundation of India, India
Nidhee Jadeja,
Imperial College London,
United Kingdom

*CORRESPONDENCE
Narendra K. Arora
nkarora@inclentrust.org

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Barriers in reaching new-borns and infants through home visits: A qualitative study using nexus planning framework

Vaishali Deshmukh[1], Shibu John[2], Abhijit Pakhare[3], Rajib Dasgupta[4], Ankur Joshi[3], Sanjay Chaturvedi[5], Kiran Goswami[6], Manoja Kumar Das[1], Rupak Mukhopadhyay[1], Rakesh Singh[1], Pradeep Shrivastava[1], Bhavna Dhingra[7], Steven Bingler[8], Bobbie Provosty Hill[8] and Narendra K. Arora[1]*

[1]The INCLEN Trust International, New Delhi, India, [2]School of Management and Business Studies, Jamia Hamdard, New Delhi, India, [3]Department of Community Medicine, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India, [4]Centre of Social Medicine and Community Health, Jawaharlal Nehru University, New Delhi, India, [5]Department of Community Medicine, University College of Medical Sciences, New Delhi, India, [6]Department of Community Medicine, All India Institute of Medical Sciences, New Delhi, India, [7]Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India, [8]Concordia–Architecture, Planning, Community Engagement, New Orleans, LA, United States

Background: Home visitation has emerged as an effective model to provide high-quality care during pregnancy, childbirth, and post-natal period and improve the health outcomes of mother- new born dyad. This 360^0 assessment documented the constraints faced by the community health workers (known as the Accredited Social Health Activists, ASHAs) to accomplish home visitation and deliver quality services in a poor-performing district and co-created the strategies to overcome these using a nexus planning approach.

Methods: The study was conducted in the Raisen district of Madhya Pradesh, India. The grounded theory approach was applied for data collection and analysis using in-depth interviews, and focus group discussions with stakeholders representing from health system (including the ASHAs) and the community (rural population). A key group of diverse stakeholders were convened to utilize the nexus planning five domain framework (social-cultural, educational, organizational, economic, and physical) to prioritize the challenges and co-create solutions for improving the home visitation program performance and quality. The nexus framework provides a systemic lens for evaluating the success of the ASHAs home visitation program.

Results: The societal (caste and economic discrimination), and personal (domestic responsibilities and cultural constraints of working in the village milieu) issues emerged as the key constraints for completing home visits. The programmatic gaps in imparting technical knowledge and skills, mentoring system, communication abilities, and unsatisfactory remuneration system were the other barriers to the credibility of the services. The nexus planning framework emphasized that each of the above factors/domains is intertwined and affects or depends on each other for home-based maternal and newborn care services delivered with quality through the ASHAs.

Conclusion: The home visitation program services, quality and impact can be enhanced by addressing the social-cultural, organizational, educational, economic, and physical nexus domains with concurrent efforts for skill and confidence enhancement of the ASHAs and their credibility.

KEYWORDS

home visitation, new-born care, community health worker (CHW), ASHAs (accredited social health activists), India, nexus planning

Introduction

Home visitation is an effective and community-wide acceptable model to provide intensive care during pregnancy, childbirth, and postnatal care to improve maternal and child health outcomes (1, 2). Most of the home visitation programs are grounded on the ecological theory suggesting that the children develop in multi-layered environmental conditions (3). It links the parents-child-family and the health systems (4) and is a cost- and time-effective intervention (5, 6) that empowers skill, knowledge, and awareness of the mother on childcare, early identification of sickness, and care-seeking (7, 8), thereby improves the maternal and neonatal outcomes (9, 10).

ASHAs (Accredited Social Health Activists) are the community health functionaries stationed in the villages (1 ASHA per 1,000 population) and over a million ASHAs are working in 600000 villages across India (11). As part of the Janani Shishu Suraksha Karyakaram (JSSK, June 2011) (12) and Home Based Newborn Care (HBNC, August 2011) programs, ASHAs have been entrusted to visit pregnant women, facilitate institutional delivery, and make 6–7 home visits during the post-natal period to empower the mothers and mobilize the beneficiaries to health facilities, when required (13). Later in 2013, as part of the Norwegian India Partnership Initiative (NIPI) (14), the Home-Based New-born Care Plus (HBNC plus) program was piloted in four states of India (Rajasthan, Madhya Pradesh, Bihar, and Odisha). The HBNC Plus involved four more home visits for the infants after the postnatal period, at ages 3, 6, 9 and, 12 months to provide counseling for age-appropriate feeding, hand washing, regular play and, communication for early child care and development (ECCD), immunization, prophylactic oral rehydration solutions (ORS) and Iron and folic acid (IFA) distribution and growth monitoring.

Studies have shown that when an adequate number of home visits are made for newborns and infants accomplishments of the tasks assigned to community health workers lead to both better physical and cognitive development and early identification of sickness. High-quality home visitations also decreased the mortality and morbidities in this age group (15–17). An ASHA evaluation across seven Indian states demonstrated heterogeneity in-home visitation patterns both in terms of number and quality of visits (18). Mothers rated the performance of ASHAs as poor for advice/counseling regarding obstetric danger signs, neonatal assessment and, care in Karnataka, India (19). The internal program evaluation document of the NIPI program also showed that home visitations by ASHAs under HBNC and HBNC Plus programs were both inadequate and poor in quality and <10% of sick young infants were mobilized by the frontline workers to health facilities (20). The barriers to timely home visitation and high-quality service delivery by the ASHAs are only partially understood. The social, cultural, and personal constraints have not been comprehensively researched in most of the studies, and the focus was generally limited to programmatic challenges (21). The HBNC Plus program evaluation highlighted the difficulty of translating the inputs, such as training and incentives into the desired outputs, such as home visits, both quantity- and quality-wise (20). The current study was therefore undertaken to document the barriers to completion of expected home visitation and quality of service delivery by the ASHAs as part of the HBNC (during the first six weeks after birth) and HBNC Plus programs (during the post-neonatal period through the first year of life) in Raisen district of Madhya Pradesh, India.

We applied the nexus planning framework (NPF), which is based on 360-degree assessment of the challenges, interlinkages, synergies and, trade between the challenges with emphasis on cross-sectoral sustainability and enhancing the socio-economic-cultural-and organizational resilience against current and future barriers. The NPF method was a further refinement of the traditional formative component recognizing the importance

Abbreviations: ASHA, Accredited Social Health Activists; ANM (Auxiliary nurse midwives; AWW, Aganwadi worker; BPM, Block program manager; BCM, Block community mobilizer; CDPO, Child Development Project Officer; DIO, District immunization officer; FGD, Focus group discussion; HBNC, Home-based newborn care; IFA, Iron and folic acid; IDI, In-depth-Interviews; LMIC, Low and middle income countries (LMIC); MENA, Middle East and North Africa; NPF, Nexus Planning Framework; NIPI, Norwegian India Partnership Initiative; ORS, Oral rehydration solutions; SDG, Sustainable development goals; VHSNC, Village Health Sanitation & Nutrition Committee; WEF, Water-energy-food.

of sub-group and sub-constituencies of the stakeholders and attempts to incorporate their respective concerns, hesitancy and, fears and unique solutions (22).

Methods

Study site

The study was conducted in Raisen district of Madhya Pradesh, India from October 2016 to September 2018. Madhya Pradesh has one of the highest neonatal and infant mortality rates in the country and is one of the eight socio-economically backward states (Bihar, Chhattisgarh, Jharkhand, Orissa, Rajasthan, Uttaranchal and, Uttar Pradesh), also referred to as the Empowered Action Group (EAG) states (23). In Madhya Pradesh, HBNC Plus pilot program was rolled out by NIPI in four districts (out of 51 districts) namely Raisen, Hoshangabad, Betul and, Narsinghpur. These districts are not part of the 123 aspirational districts declared by NITI Aayog but their overall rankings for development including health indicators are in the lower one-third of all districts of the country (24). Raisen district had poor indicators for mobilization of home- delivered mother-child dyad to skilled health personnel within 48 h, and dispensing of ORS to diarrhea patients among the four NIPI districts (25, 26). The Department of Health and Family Welfare, Government of Madhya Pradesh, NIPI leadership and, the investigators jointly decided to include Raisen district for the evaluation of ASHA performance for home visitations under HBNC and HBNC Plus programs. In the district, four administrative blocks were purposively selected for the study i.e., Gairat Ganj (53 kms), Begam Ganj (78 kms), Silwani (86 kms), and Udaipur (80 kms), based on their distance from the district headquarter.

Study methods

The study had two phases data collection, analysis and, synthesis. During Phase I (formative research), we applied the qualitative research methods using grounded theory for data collection and analysis. In-depth interviews (IDIs) and focus group discussions (FGDs) with various participants were conducted at their respective locations. Phase-II: Data from Phase-I were used for conducting the multi-stakeholder nexus planning (NP) exercise.

Phase I: Formative research

Participant selection

Community engagement: Before commencing our community activities, we had a series of meetings with village leaderships (Panchayat members) in the four study blocks to explain to them the purpose and methods of the study and obtain their buy-in. We purposively selected the respondents for IDIs and FGDs ensuring the representativeness at different levels (national, state, district, and community levels) (Figure 1). We purposively selected the respondents from different stakeholder categories (home visitation beneficiaries, ASHAs, and other frontline health and Anganwadi workers residing and working in these four blocks, healthcare providers and, program managers working at block, district, state and, national levels). At this stage, the caste of the stakeholder (lower/backward and upper/forward) was neither considered for the selection nor was not recorded to avoid any bias. The investigator group decided following definitions to define beneficiary mothers as utilizers of the home visitation by ASHA: (a) under HBNC program: 4 or more home visits done during 1.5 months after birth; (b) under HBNC Plus program: 2 or more home visits done between 3 and 12 months of age. Non-utilizers had not received any home visits. The quality of each home visit was assessed with reference to the program guidelines (13, 27). A prior appointment was taken with the interviewee before all interactions and during the face-to-face interaction.

Data collection and analysis

We collected data using pretested semi-structured IDI and FGD guides developed by the investigators/authors, a multi-disciplinary team. A team of four female social scientists trained in qualitative data collection conducted the IDIs and FGDs at places convenient to the interviewee and no observer was allowed. The IDIs and FGDs were conducted in the local language (Hindi) and audio recorded with consent. Some of the IDIs with health managers at the state and national level were in English; these were also recorded. Study investigators (VD, AP) conducted the IDIs at the national, state and district levels and facilitated the FGDs. Senior researchers (NKA, VD, AP, and SJ) with at least 15 years of experience in qualitative research, supervised data collection, and analysis. Most of the IDIs and FGDs lasted for about one hour (range 50 to 120 min).

All IDIs and FGDs were transcribed (i.e., Hindi) and then translated into English. The transcriptions/translations of all IDIs and FGDs were entered using INCLEN qualitative data analysis software (IQDAS) (28) for systematic organization and retrieval of data for analysis. During quality assessments, four IDIs were rejected due to incompleteness (one) and poor quality audio (three). We adopted the grounded theory (29) approach for data analysis. All the IDI and FGD transcripts were carefully read by two trained social scientists and reconfirmed by a senior author (VD), to interpret the data. The researchers inductively analyzed the data using the following steps: (i) free-listing and open-coding of the responses and marking the relevant/introductory statements for use as quotable quotes; (ii) axial coding of the responses keeping in mind

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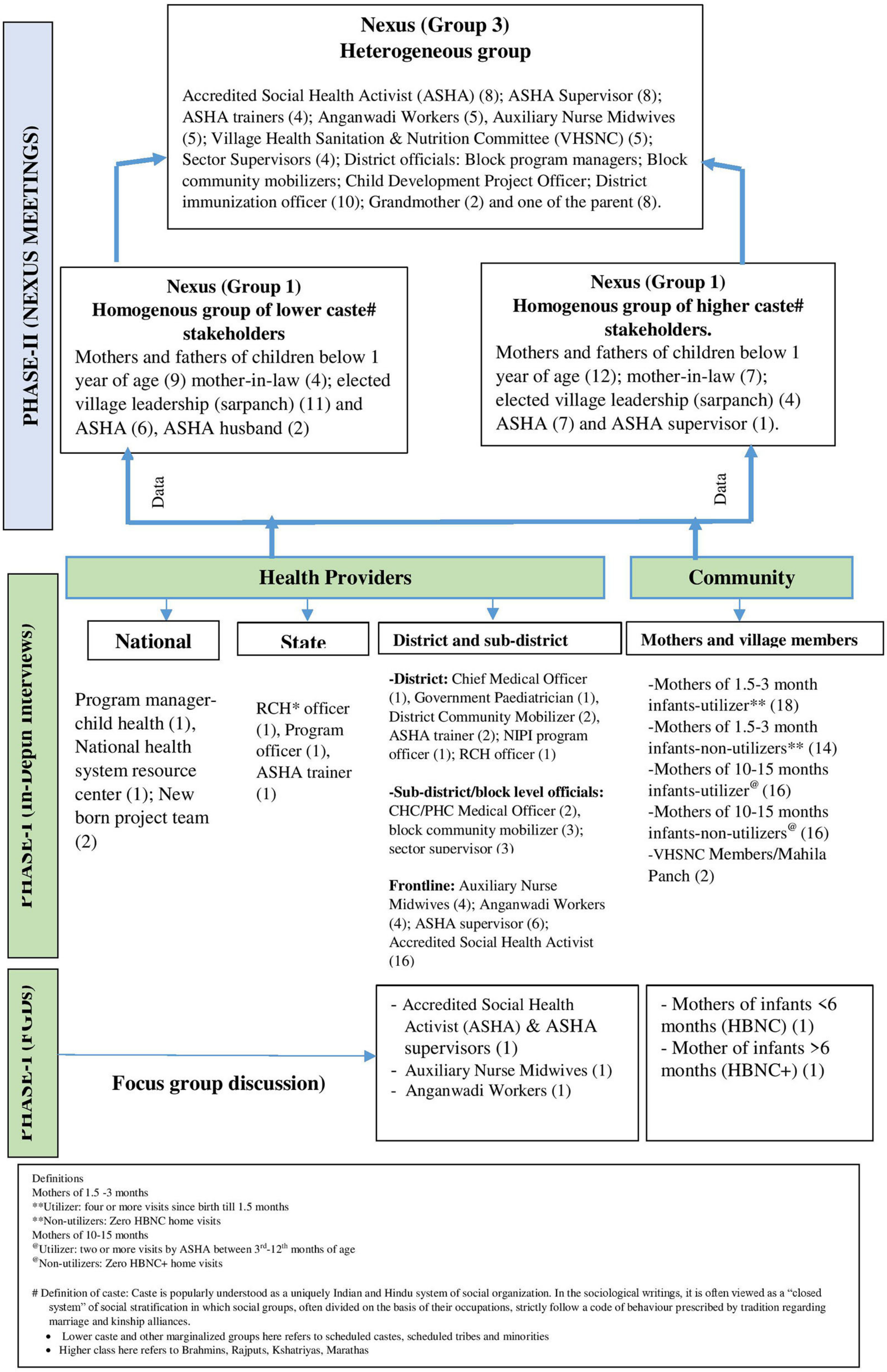

FIGURE 1
Stakeholders involved in the study.

the connection/relationship between free-listed responses/small units, and (iii) develop selective codes (wherever applicable) for the clusters of axial codes communicating common theme. The emerging patterns/themes from the responses, helped the researchers to interpret the ASHA's functioning in the light of the different challenges. The emerging codes and themes were regularly discussed with the senior author (NKA) to resolve inconsistencies. All analytic steps were followed (open, axial, and selective coding) consistently to have inter-coder reliability and stability, and reproducibility (30). Data quality was ensured by triangulating data collection methods at two levels-across methods and across respondents (trustworthiness). The findings were expressed semi-quantitatively using qualifiers to express findings systematically: very few (<10%), some (10–24%), about half (25–49%), the majority (50–75%), most (76–89%), and almost all (>90%). The quasi-quantitative expressions are based on how many times the code was mentioned (28, 31).

Phase II: Nexus planning approach

Nexus planning framework (NPF)

Nexus approach is currently used in a large number of sectors to define solutions to complex, multidimensional, and layered challenges. Under the nexus approach, interlinkages, synergies, and trade-offs are analyzed, with the aim of identifying solutions and improving the performance of ecosystems. Thus, nexus planning emphasizes cross-sectoral sustainability and enhances socio-economic-cultural-organizational resilience against current and future challenges. We have used NPF as a participatory co-creation process to ensure ownership of all stakeholders including their sub-constituencies in decision-making and bringing about accord among all stakeholders including the program implementers to improve the performance of ASHAs, particularly for home visitations under HBNC and HBNC Plus program. NPF systematically focuses on the challenges and attempts to identify the possible solutions under five nexus domains: social-cultural, economic, physical, organizational, and educational (22, 32–34) (Figure 2).

Process of nexus planning approach

The nexus planning process had three steps after the initial formative research component using qualitative methods (Phase I), which identified the barriers and facilitators to the home visitations by the ASHAs from a large number of stakeholders including the mothers and ASHAs (Figure 1). The data from Phase-I were analyzed and organized according to the five nexus domains for sharing with different stakeholders.

Nexus planning step-1

An extensive discussion was held between the investigators, field staff, and Panchayat members to identify essential sub-groups/constituencies of all stakeholders, which had different perspectives and social dynamics at the ground level. Through the discussion, then it was decided to conduct three nexus meetings/consultations considering the caste groups of the community and the frontline workers and larger community of service providers; one each including the representatives from lower and higher/upper castes (as per the local knowledge) and the third with mixed representatives drawn from all caste groups.

Nexus planning step-2

Each of the caste-specific nexus planning meetings/consultation had 20–30 participants drawn from the same caste group (community and parents from all the four blocks, ASHAs from the respective blocks and two program managers from the district). The meetings were facilitated by the authors. The objectives of these nexus planning meetings/consultations were to discuss the findings from Phase-I (formative research); validate the sub-group specific observations emerging from the data analysis; identify the challenges categorized according to the nexus domains and suggest solutions appropriate for their respective caste groups.

Nexus planning step-3

Following the caste-specific nexus planning meetings/consultations, the final larger heterogeneous stakeholder group consultation (59 participants) was organized to bring synergy between the perspectives of the two sub-groups, smoothen the points of disagreement and develop final recommendations for improving the performance of the ASHAs in the communities. This nexus planning method is a further refinement of traditional formative components recognizing the importance of sub-group and sub-constituencies of the stakeholders, bringing about synergies, accord and identifying the points of negotiations so that the recommendations incorporate their respective concerns, hesitancy and fears, and unique solutions.

Structure of nexus planning meetings (NPMs)

The nexus planning process was facilitated by two experts, who are the innovators of the process (BH, SB) and authors having experience in community engagement. The participants for nexus planning meetings included: (i) community stakeholders engaged in the process of home visitation directly or indirectly i.e., mothers, family members, village

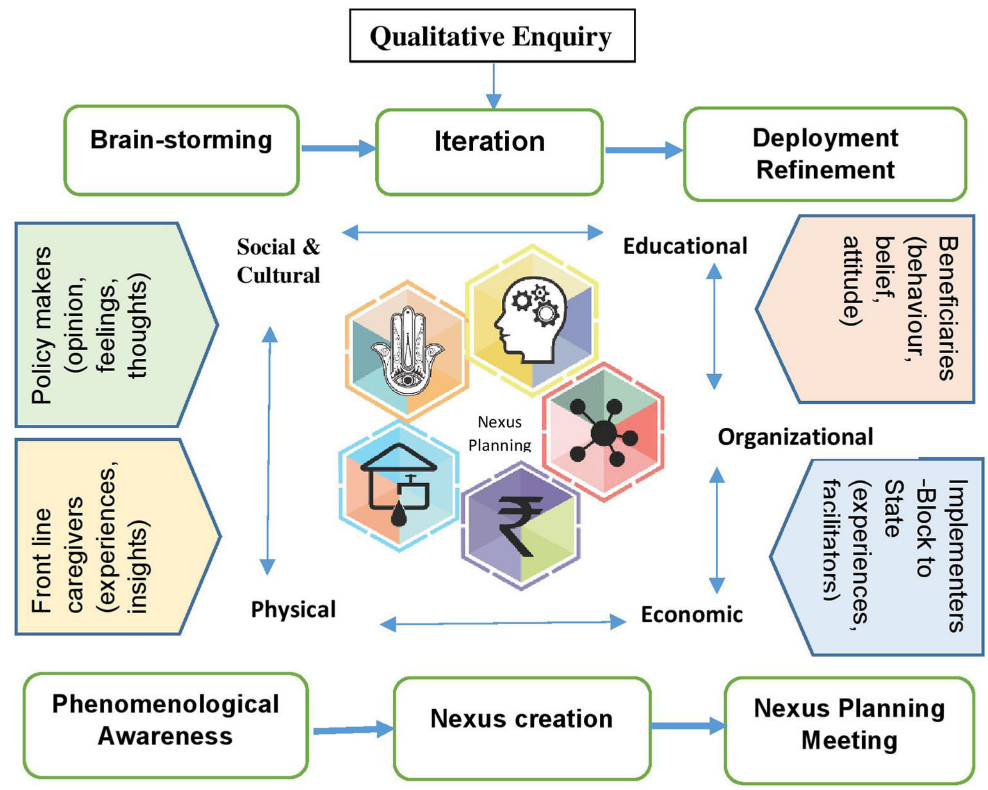

FIGURE 2
Nexus framework.

leadership (religious, social, and cultural); (ii) elected village leadership (Panchayat - local self-Government), Village Health, Sanitation, and Nutrition committee (VHSNC) members; (iii) representatives from education, revenue, and administration departments; (iv) respondents from the health department–ASHAs, ANMs, doctors from PHC/CHC and Chief Medical Officer of the district, ASHA supervisor; and (v) department of women and child welfare-AWWs. Three NPMs were organized: two preliminary NPMs considering the social demographic sensitivity [the community stakeholders were purposely drawn from low (first NPM) and high castes (second NPM)] and the third with a mix of community and representatives from the health system (Figure 1). No such differentiation was done for the healthcare providers and frontline workers for these NPMs.

First (32 participants; community members drawn from 15 villages) and second (31 participants; community members drawn from 8 villages) NPMs reviewed the findings of the IDIs and FGDs and indicated their views about the correctness of the data and its interpretation. The rationale of giving importance and hearing to all the sub-group stakeholders/constituencies brought out items and matters which required joint discussion to arrive at a mutually acceptable way forward. The challenges faced by ASHAs from forward and backward communities were different and had to be handled in a manner that required suggestions from both sides.

The third NPM (59 participants; community members from 22 villages) discussed the barriers and strategies for overcoming these in a harmonized, negotiated, and comprehensive manner. Each NPM had a similar work process. The objective of the initial plenary of 60 min, was to apprise the heterogeneous audience of the perceptions of the diverse sub-group stakeholders and emerging themes that required careful attention. The group was divided into 3 smaller groups and each comprised mix of community sub-groups/constituencies and geographies of the district along with health providers. Nexus planning charts were used primarily to keep the discussion on track document discussions according to specific domains, and develop final recommendations for improving the performance of the ASHAs in actual field settings (Figure 3). Finally, the plenary session of 90 min summarized the findings from all the sub-groups. The total duration of these meetings was approximately 3.5 to 4 h (including conduction). During the final plenary session, the three groups came together to build a consensus about the barriers and solutions and organized

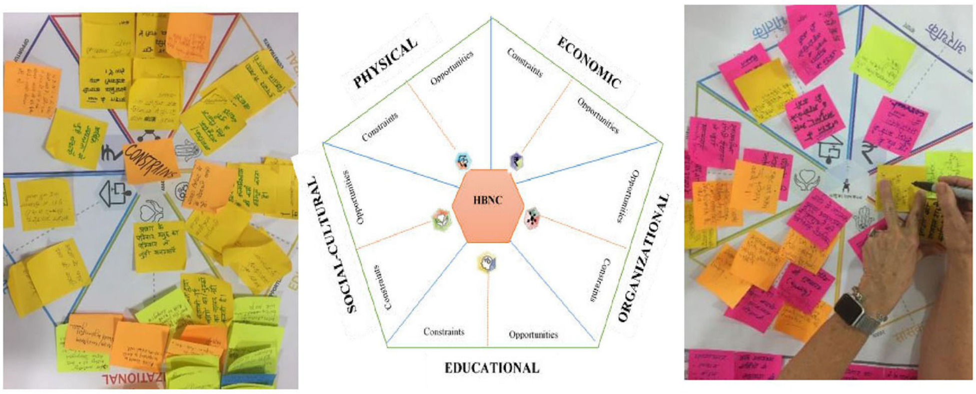

FIGURE 3
Nexus chart.

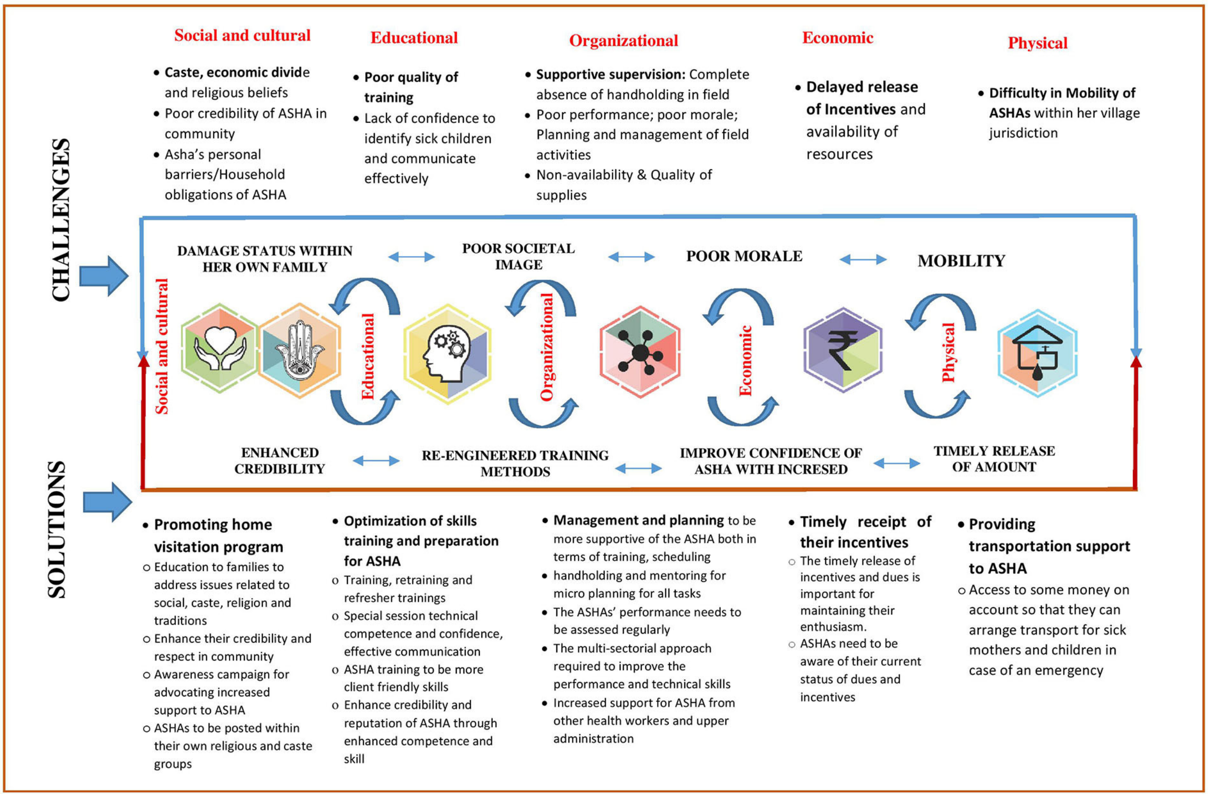

FIGURE 4
The challenges and solutions to improve ASHAs postnatal home visits.

into the NPF. The summary also identified action for different stakeholders to improve the frequency and quality of home visitation and sustain these during the immediate post-partum period (HBNC period) and up to 15 months of age (HBNC Plus period).

Collation and interpretation of NPMs

The NPM facilitators noted down the observations and comments of every participant on 'post-it/sticky notes' and collected these on the nexus domain chart. The findings from the first and second NPMs were shared with 3rd large group

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NPMs. The final plenary of the 3rd NPM helped in the co-identification of the barriers, and co-creation of the solutions and recommendations under the five nexus domains i.e., socio-cultural, physical, organizational, economic, and education.

Results

Phase I (qualitative data)

Figure 1 and Table 1 provide the distribution of stakeholders, and demographic profile of mothers and frontline workers participating in Phase-I of the study. A total of 119 IDIs were conducted: mothers (64), ASHAs (16), Auxiliary Nurse Midwives (ANMs) (4), Aganwadi workers (AWW) (4), ASHA supervisors (ASHA Sahyogini) (6), VHSNC members (2) and health system representatives at block, district, state and national levels (23). We also conducted five FGDs: one each with mothers of an infant under <6 months old infants (for HBNC) and one with mothers of an infant 6 months to 15 months for (HBNC Plus program); one with ASHAs and Asha supervisors; one with ANMs and one with AWWs to supplement the IDIs for data saturation and data triangulation (Figure 1).

Data from Phase-I has been organized under the nexus domains with the emerging themes and sub-themes along with an illustrative statement from the participants.

Social and cultural factors

Theme-1 caste, economic divide, and religious beliefs

The majority of the state and district level stakeholders, ANMs, and approximately half of the ASHAs identified socio-economic divide and caste/religion-based discrimination making the home visitations difficult and the reluctance of families to accept the health and wellness messages for childcare and more so for male children. Socio-cultural beliefs such as seclusion of post-partum mother and child and belief in the tradition of the'evil eye effect' also made it difficult for ASHAs to deliver the desired services.

> *"Some refuse to put the child in the weighing bag. They say that you took the weight of the Muslim child, the Scheduled tribes (ST) Child and now you will put our child in the same bag" [ASHA Sahyogini]*
> *"She is from a rich family. Why will she will come to a low-income family house?" [Mother non-utilizers]*
> *"Some are Harijan (Scheduled caste), and some are Vasur (scheduled caste)?, so she differentiates. She is not comfortable coming to our house. She does not touch our child." [Mother non-utilizers]*

Theme-2 credibility of ASHA

Stakeholders from the administrative hierarchy and community perceived trust deficit and lack of respect and credibility of ASHA due to lower education status, inadequate training, and lack of confidence demonstrated while communicating with the family members. Similarly, the community questioned the ASHA's credibility, when the family experienced 'inadequate or suboptimal' services at the health facility to which ASHA referred them. Several elders in the family preferred traditional childcare methods over ASHA's suggestions. Common superstitious beliefs such as 'Sutak' (prohibitions observed during post-partum period), when the mother-neonate are confined indoors, were used as an excuse to refuse both contact/examination by the ASHA and referral. The front-line workers (ANMs, AWWs, and ASHA supervisors) perceived that it was difficult for ASHAs to convince the community and families about immunization and the associated minor side effects. Families also showed deep-rooted resistance in following advice, such as play and communication with the child and washing hands with soap, which considerably differed from their existing practices and were perceived as irrelevant to them. Approximately half of the non-utilizers mothers complained of the lack of resources required to follow ASHAs' advice. We also found a better understanding of utiliser mothers' knowledge of program components like exclusive breastfeeding, IFA syrup, hand washing, and ORS preparation when compared with the non-utilizers mothers.

> *"People doubt her motive when she visits their house again and again". [AWW]*
> *"ASHA instructs mother what all things she should follow after delivery. Family members get irritated that why she is instructing her". [ASHA Sahyogini]*
> *"We don't expect much from ASHA since she doesn't know much herself." [Mother, hard to reach]*
> *"If ASHA asks them for vaccination and child has a mild fever, then they immediately say no. Few people don't behave well with the ASHA." [ANM]*

Theme-3 personal factors and client family-related challenges of ASHA

The majority of the ASHAs felt that they were caught between their domestic (looking after children and husbands, household chores) and professional responsibilities. According to the ASHAs, the non-availability of a mother at the time of the home visit or the mother's engagements with social responsibilities posed additional challenges. Mothers were unhappy that most ASHAs did not maintain a timetable for upcoming home visits or were informed of a home visit beforehand. Many mothers went back to their natal homes after

TABLE 1 The socio-demographic characteristics of the study participants.

Mothers of children	HBNC		HBNC Plus	
	Mother utilizer [6 weeks-3months children] ($N = 18$) (%)	Mother utilizer [10-15 months child] ($N = 16$) (%)	Mother non-utilizer [6 weeks−3months child] ($N = 14$) (%)	Mother non-utilizer [10–15 months child] ($N = 16$) (%)
Literacy status of the mothers				
Illiterate	3 (16.7)	7 (43.7)	2 (14.3)	4 (25)
<5th standard	2 (11.1)	5 (31)	2 (14.3)	4 (25)
6–12 standard	12 (66.6)	4 (25)	10 (71.4)	8 (50)
>12 standard	1 (5.5)			
Mother's occupation				
Housewife	12 (66.6)	12 (75)	12 (85.7)	10 (62.5)
Working outside	6 (34.2)	4 (25)	2 (14.3)	6 (37.5)
Literacy status of the fathers				
Illiterate	3 (16.6)	2 (12.5)	2 (14.3)	3 (18.7)
<5th standard	2 (11.1)	4 (25)	-	2 (12.5)
6–12 standard	12 (66.6)	10 (62.5)	11 (78.5)	11 (68.7)
>12 standard	1 (5.5)		2 (14.3)	
Father's occupation				
Farming (own farm)	4 (22.2)	6 (37.5)	5 (35.7)	8 (50)
Farming (laborer)	10 (55.5)	7 (43.7)	7 (50)	8 (50)
Self-employed (Shopkeeper/tailor/carpenter)	4 (22.3)	3 (18.8)	1 (7.14)	-
Government job	-	-	1 (7.14)	-
Type of family				
Extended	13 (72.2)	8 (50)	8 (57.1)	6 (37.5)
Joint	2 (11.1)	5 (31.2)	1 (7.1)	6 (37.5)
Nuclear	3 (16.7)	3 (18.7)	5 (35.7)	4 (25)
Religion (Hindu)	18 (100)	16 (100)	14 (100)	16 (100)
Frontline health functionaries	ANM* ($N = 4$) %	AWW* ($N = 4$) %	ASHA* ($N = 16$) %	ASHA Supervisor ($N = 6$) %
Age				
<30 years	-	-	6 (37.5)	3 (50)
31–40 years	1 (25)	2 (50)	6 (37.5)	3 (50)
>40 years	3 (75)	2 (50)	4 (25)	
Marital status (Married)	4 (100)	4 (100)	16 (100)	6 (100)
Education				
<10th Standard	-	-	11 (68.8)	
10–12th standard	1 (25)	3 (75)	4 (25)	3 (50)
>Graduate	3 (75)	1 (25)	1 (6.3)	3(50)
Years of working in current position in sub-centre/area				
<5 years	-	-	4 (25)	6 (100)
5–10 years	-	1 (25)	12 (75)	-
>10 years	4 (100)	3 (75)	-	-
Focus group discussions (FGD) ($N = 5$)	ASHA* (8) (1-FGD)	ANM* (8) (1-FGD)	ASHA* Supervisors (8) (1-FGD)	Mothers of infants (10+10) (2-FGD)
Age (in years)	25–40	30–40	30–40	20–32
Working in current position in sub-centre/area (in years)	5–10	10–12	5–10	-

* Accredited Social Health Activist (ASHA); *AWW: Anganwadi Worker; *Auxiliary Nurse Midwives (ANMs).

childbirth for 6–12 weeks. As a result, either the HBNC visits remained incomplete, or HBNC Plus visits began late.

> *"I was having an issue with my mother-in-law because she repeatedly kept asking where I went. I have to tell her that I have to measure weight by going house to house as an ASHA responsibility. Then she allows me to go." [ASHA]*
> *"Other issues are mother goes to her maternal place along with child or if the child is underweight then she is referred to hospital and sometime ASHA is herself tied up with some work in such cases she is not available to make home visits." [ASHA Sahyogini]*

Educational factors

Theme-4 capacity building

The health supervisors expressed concern about the ASHA training including residential training (staying away from the residence), curriculum design and its poor translation; and organization of practical skill training. However, most ASHAs and ASHA supervisors did not point out any difficulty in attending residential training. ASHAs and their supervisors reported that the training was insufficient and unsuitable; difficulty in comprehending technical terms related to many health and medical science by the ASHAs with less formal education, the content of the curriculum material, and the pace of knowledge imparting procedures in real-life situations.

> *"As and when we come back home, then we cannot learn further anything under the supervision and become busy with village and family chores. And after some time, many forget their training." [ASHA]*
> *"Personally I feel ASHA is not a proper person to identify neonatal sepsis. We have trained we have to define the criteria for what are the danger signs and how to identify them. I think it is difficult for women from the field with a limited knowledge." [State Officer]*
> *"ASHAs hardly retain about 50% of training." [ASHA Sahyogini]*

Theme-5 communication and technical skills

One of the most critical determinants of ASHA's credibility and acceptability in the community was its technical competence and communication skills. The ASHAs' inability to recognize sickness in children and the rationale and basis of nutritional and play therapy made it challenging to communicate messages correctly, effectively, and confidently. State and district level stakeholders acknowledged the poor quality of home visits because of the ASHAs' technical and communication competence challenges despite frequent contact. Although half of the ASHAs responded that they don't experience any difficulty performing HBNC/HBNC Plus responsibilities, almost a similar proportion accepted that they encountered problems while making home visits. ASHAs acknowledged that some of the poor response from mothers and family members was on account of their inability to communicate clearly and effectively. Some ASHAs reported having difficulty in performing technical tasks such as measuring temperature, weighing new-born, and making growth charts.

> *"I don't have enough knowledge to know whether he has a fever or not. We make an idea by seeing whether he is playing or not. [ASHA]*
> *"She is not able to explain when and how much IFA syrup is to be given and why it should be given". [Block Medical Officer]*
> *"ASHAs hardly retain about 50% of training." (Echoed by many ASHA Sahyoginis)"*
> *"She is unable to form connectivity. When she goes for a home visit, she talks about general household things such as cooking and does not discuss health services. They forget total about health and wellness issues. It is the main gap." [District Level ASHA Trainer]*

Organizational issues

Theme-6 supportive supervision

ASHA supervisors claimed that they monitored and supported the ASHA's activities. State and regional managers, however, acknowledged that the supervision of ASHAs was both poor and unsatisfactory because of vacancies in the supervisory cadre (ASHA Supervisors). The HBNC/HBNC Plus performance formats/reports were reviewed infrequently and supervision was of limited utility. The program managers strongly contended that state and district-level officers should also visit the field to understand and address the managerial bottlenecks. Block and community-level stakeholders mentioned the availability of a limited mobility budget for monitoring was also a hurdle in program monitoring.

> *"Supportive Supervision is one of the weakest links in-home visitation, which was the strongest in the Abhay Bang Gadchiroli project." [National level stakeholder].*
> *"At the block level, we have to check the filled forms; we are unable to check it properly due to a high number of forms being submitted at the block level every month. It becomes difficult to review all the forms properly." [Block community mobilizer]*

Theme-7 planning and management of field activities

ASHAs, their supervisors, and senior officers consistently accepted that the tasks assigned to ASHAs were complex.

The ASHAs were imparted limited exposure to planning and prioritization exercises during training. Not infrequently, ASHAs re-prioritized their work based on directives from higher-ups for health and non-health exigencies beyond the planned activities. Vacancies and rapid turnover among ASHAs and vacant positions in supervisory cadres added to poor planning and management.

> *"ASHA has many other responsibilities, prioritization and non-adherence to the schedule should be seen in that context." (Echoed by many ASHA Sahyoginis)*
> *"There are 5-10 percent vacancies for the post of ASHA Sahyogini, ASHA, and BM (block mobilizer)" [Programme Officer]*

Theme-8 availability and quality of supplies

Irregular and insufficient supply of products (such as ORS and IFA syrup) and stationery adversely affected the HBNC/HBNC Plus related functioning of the ASHAs. The managers attributed this to distribution process-related challenges and delays by ASHAs to indent the supplies.

> *"Last year in January, my BP and weighing machine were not working. So I deposited in last February, and I got this February." [ASHA]*

Economic issues

Theme-9 incentives and availability of resources

ASHAs are remunerated on the basis of the completed tasks (such as vaccination or home visits). Most ASHAs complained about the delay in receiving the incentives. The factors identified for the delays included: late receipt of funds, inability to fill the records appropriately, and refusal by the families to comply with their advice regarding immunization and sickness and hospital referrals. On the other hand, supervisors pointed to the challenges in releasing the incentives due to incorrect and incomplete maintenance of records and mismatch between claims and feedback from the field; shortage of funds was infrequent and not considered as significant concern. While most of the ASHAs and ASHA Supervisors reported receipt of only 50 percent to 70 percent of their entitled monthly incentives, the managers at the district level didn't agree with it and claimed that the full amount was distributed. The family members of ASHAs were reportedly unhappy about the lesser amount of incentives, delay in payments, and being paid less than other frontline workers (e.g., Anganwadi workers); which pose challenge in obtaining adequate support from their own family itself to perform the duties.

> *"We get money after 2 or 3 months, and it's not monthly. Everyone gets after this much time. When we say this to sir, he says that I am the only person managing it, so delay happens, and there is no such work for which we should pay early." [ASHA]*

Physical issues

Theme 10 – ASHA's mobility within her village jurisdiction

The ASHAs and several program managers at different levels acknowledged the hurdles related to reaching outlying and hamlets, tribal areas, and areas with hilly terrain. Few of the ASHAs were not from the same village communities (though this is an essential mandate) and therefore needed to travel to their place of work.

> *"Tribal population is living in far off areas. So need a strategy for better reach". [NIPI Programme Officer]*
> *"Some villages are too big, and houses are scattered. The area might be split into smaller ASHA jurisdictions." [PHC Medical Officer]*

Nexus planning meetings (NPM)

The details of the discussion held during the preliminary two caste-specific NPMs are presented in Table 2. The purpose of the NPMs was to identify the strategies to negotiate these challenges of the constructs by each of the social groups and help ASHAs better accomplish their other tasks in their community settings. The emerging themes and potential solutions were noted for both caste sub-groups. Most of the obstacles and the suggested approaches to overcome were similar across the groups, the lower and higher caste groups. The lower caste groups came up with suggestions to mitigate the caste and religion-related biases through awareness generation about the purpose of ASHAs' home visitations. Awareness regarding the value of home visitation and the role of ASHAs were considered essential for men from all communities, elder women who are particularly prejudiced, and the village leadership. The higher caste groups made additional recommendations on earning respect for ASHA by imparting her technical competence and good communication skills that would facilitate acceptance and performance. Through these collective efforts and discussions, we synthesized a broad range of views echoed by participants of the NPMs. The recommendations facilitated building contextual ownership and finding solutions to the barriers in making home visitation by the ASHAs.

The larger NPM group framed the recommendation at two levels: (i) administrative and organizational level; and

TABLE 2 Preliminary nexus planning meetings with stakeholders (community, families, parents, ASHAs) separately with the lower caste (LC) and higher caste (HC) groups: summary of issues influencing home visitation by the ASHAs under HBNC & HBNC Plus programs.

Domains	Domain specific challenges	LC	HC	Broad potential solutions	LC	HC
Social and cultural						
Caste, economic divide & religious beliefs	Challenges due to cultural rituals/ social caste & religion conflicts /Social caste and religion based challenges	√	√	Men of the household must be involved more in negotiating such barriers.	√	X
	Higher caste families don't allow ASHAs to handle their child/ low caste ASHAs discriminated, not allowed into upper caste house	√	√	There should be multi-caste and religion meetings to discuss such issues in addition to the participation by the Panchayat.	√	X
	Differentiation between different social & religious classes / no acceptance of food and water from lower caste/poor	X	√	Similar caste/community should hold meetings and find ways to negotiate such barriers with members of the other community.	√	X
	Weighing babies from different castes and religion on the same weighing bag- makes it difficult for ASHAs to do her tasks	√	X	Panchayat should encourage higher caste ASHAs to visit all houses without discrimination	X	√
	Caste discrimination by women is more common compared to men of the same caste	√	√	Involve Panchayat in helping ASHAs overcome caste barrier	X	√
	Elder women (e.g., Mothers in law, grandmothers) discriminate more as compared to younger women	X	√	Higher designation of ANM makes her immune to caste discrimination; similarly ASHAs can be accorded higher official status	X	√
	During menstrual period women are not allowed to touch babies	√	√	Local women's group can help and explain to the families from all social sections to facilitate home visits.	X	√
	Social beliefs regarding restricted contact with recently delivered women and their babies	X	√	Panchayat members and Sarpanch can help ASHAs in visiting the households that are resisting and are a challenge	X	√
	Families trust traditional home remedies over ASHAs' advice / families believed in traditional home remedies	√	√	Families encouraged to adopt good traditional practices along with ASHAs advice for child's sickness and wellness	X	√
	Pressure from same community and clan members to maintain social and religious discrimination	X	√	To reduce the cast and social barriers, there is need for demonstration from the top political and administrative levels	X	√
	Some high caste women prefer home deliveries due to their superiority complex	X	√	Awareness about the high value for institutional deliveries for reluctant families	X	√
Personal barriers of ASHAs client family related challenges	Lack of support from ASHA's family - her husband, in-laws and other family members to work in their villages for health related issues	√	√	All family members need to be oriented on the ASHAs tasks, its importance to community health and need of home visitations for the wellbeing of both the mothers and their babies	√	X
	Time constraint and pre-occupation with their household works, looking after children, husband, family members and cattle	√	√	If incentive is received in timely manner, and ASHAs are considered as contributing to the family resources, getting the support from ASHAs' family members including need to go out during odd hours shall be easier	√	X
				Mothers in law and other members help ASHAs to share responsibilities in the household chores	X	√
				Panchayat members and Sarpanch can discuss the problem with the male members and elders of the families who are interfering the ASHAs activities vis-à-vis their need at household front	√	√

(Continued)

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TABLE 2 (Continued)

Domains	Domain specific challenges	LC	HC	Broad potential solutions	LC	HC
	Adverse social comments about ASHAs' work from their co-villagers and neighbors	X	√			
Credibility	Family & community do not have faith in ASHAs' activities and home visitations	√	√	ANM/MO and block level personnel use the same and endorse the messages and activities of ASHAs to the families and community in groups	X	√
				ASHAs respond to the calls and requests from households and mothers at all times	X	√
				ASHA Supervisor and other supervisors can visit some of the households which do not have trust and confidence on ASHAs technical competence and endorse their activities	X	√
	Some educated people do not consider ASHA's visit as important one; little trust on her technical competence	√	X	Beneficiaries of the service should motivate other members of the community to take the service, e.g. mothers in law motivate other elder women to follow ASHAs advices which did good to their families, women and children	X	√
	Poor respect of ASHAs based on the economic status of the families being visited during home visits	√	X	ASHAs should talk to both the mothers and grandmothers (mothers-in-law) together or separately for clear and consistent messaging; relationship between the two might influence communication and acceptance of the advice if given to only one of them	√	√
	Families/Clients which accepted immunization and institutional delivery advices of ASHAs many times get the honorarium late	√	X	Health department should particularly be cognizant of prompt release of the incentive money for the families/Clients for improving the credibility of ASHAs	√	X
Educational						
Inadequate ASHA skills & training	Inadequate and inappropriate of ASHA Training Program: limited technical competence and skill – training needs to better alignment with literacy and exposure level of the ASHAs	√	√	More the educational qualification, technical skill - more the respect for ASHAs; their credibility and respect shall increase in the community they serve and reduce discrimination	√	X
	ASHAs communication does not give trust and confidence to the families about the advice and referral to health facilities	√	√	Illiterate and less educated ASHAs should be changed	√	X
		√	√	A more knowledgeable person e.g. ANMs can accompany ASHAs occasionally; skilled ASHAs can also be used for peer training	√	X
				Emphasis on better and more comprehensive ASHA training as per the local realities; ASHAs must specially be skilled to identify red-flags/sickness in young infants, children and postpartum mothers	√	√
				Structured re-training for poor performing ASHAs before looking for their replacements	X	√

(Continued)

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TABLE 2 (Continued)

Domains	Domain specific challenges	LC	HC	Broad potential solutions	LC	HC
	Many ASHAs do not have HBNC plus training/ Training of new ASHAs is delayed	√	√	Ensure that all new recruits are trained and not inducted in to service straight away	√	√
Organizational						
Planning & Management of field activities	ASHAs did not plan their field work and home visitation; home visits were many times surprises to the mothers and other members of the family and therefore they did not get the attention and welcome ASHAs expected Lack of planning led to missing of home visits Lack of planning also affected all other public health activities of ASHAs No infrequently ASHAs re-prioritized their work based on directives from higher-ups for emerging health and non-health exigencies and missed home visits	√	√	ASHAs need to learn planning of home visitations; mothers in poor households are busy with too many activities including income generating activities and therefore some kind of prior information is necessary for the households. Mothers said if they knew the expected time of visits, they could telephone and call the ASHAs for the schedule visits.	√	√
	Home visitation tasks assigned to ASHAs are complex and are expected to impact community behavior toward health and wellness	√	√	The understanding of ASHAs should be clear and unambiguous so that she can impart the messages consistently and with confidence	√	√
	ASHAs are not able to do some home visits because the houses are located in outlying areas of villages – inhabited by low cast families	√	√	Involve Panchayat to encourage home visits by the ASHAs and not missing particularly in high risk populations Decrease the population size under ASHAs (if possible) in these situations	√	X
Supervision and mentoring	Lack of support from other frontline workers viz. AWWs, ANMs, ASHA Supervisor (Sahyognis) Involving and seeking community support	√	X	The department formally enlists the Institutions like VHND and VHNSC oversee that other frontline workers support ASHAs' work and facilitate activities in some of the households that are reluctant to participate and cooperate ASHAs' activities	√	√
				ASHA Supervisor should visit the village more frequently and accompany ASHAs at least for some home visits every month	√	X
				ASHA Supervisor should call a meeting of all ASHAs and bring the problem to the notice of elected village head (Sarpanch) (involvement of Sarpanch to increase social accountability)	X	√
	Lack of communication between ASHA and higher officials	X	√	ASHAs must bring her problems to the notice of the medical officer of the PHC/CHCs	X	√
Economic						
Incentive & availability of resources	ASHAs' families are not happy about ASHAs working for small amount of money, which is also not received in time	√	√	Consider higher incentives for ASHAs; ASHAs wanted fixed salaries and not honorarium; this factor was cited as an important reason for the noncooperation of ASHAs families	√	√

(Continued)

TABLE 2 (Continued)

Domains	Challenges	LC	HC	Solutions	LC	HC
	ASHAs complained of not receiving their full due in time	√	√	If ASHAs get their dues completely and timely manner, their performance was likely to improve including home visitation; more support from families to travel at odd times with patients/pregnant women	√	√
	ASHAs cannot fill the claim forms/ delay in filling forms/poor maintenance of the records	√	X	ASHAs need regular handholding and help in filling the claim forms timely and correctly so that incentives are released fully and promptly	√	X
Travel & Communication Issues	No flexible funds available for ASHAs to hire vehicle for pregnant women/sick children in emergency/re-imbursements for telephone calls/SIM cards delayed	X	√	Money/call time for ASHA may be given in addition to SIM cards	X	√
Physical						
Transportation & Location Issues	ASHAs are unable to make home visits and travel with mothers and children to at odd hours; non-availability of transport facility to cross water channels between hamlets of a village	√	√	ASHAs' access to 108 in a manner that facilitates her mobility at all times and possibility of giving her flexible mobility funds	√	√
	At some places, the ASHAs are from villages different from their place of work; this is against the philosophy of ASHAs role as community worker. These ASHAs have frequent complaint of mobility and transport facilities	√	√	ASHA should be selected from the same village and not from a far off place/ Each village must have its own ASHA	X	√

Light Pink Color – Both the groups raised home visitation issues either as the challenge/barrier and or a potential solution.
Green – High caste group identified the issues either as the challenge/barrier and or a potential solution.
Blue – Low caste group identified the issues either as the challenge/barrier and or a potential solution.
ASHA, Accredited Social Health Activist; ANM, Auxiliary Nurse Midwife; AWW, Anganwadi Worker; MO, Medical officer.

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(ii) community/family level. Task-oriented skill-building of ASHAs along with frequent re-orientation through supportive supervision and handholding was considered essential to improve ASHA performance, get her rightful place in her own family and the community, and even reduce caste-based prejudices. This will require re-engineering of the whole training curriculum in a manner that is aligned to the objectives of the HBNC and HBNC Plus programs. The ASHA was expected to prepare a micro-plan for her activities and communicate preventive, promotive, and curative knowledge to the families with confidence and conviction in their homes and community settings. Equally essential was to release the incentive money rightfully due to the ASHAs in a timely and regular manner. The health system was also asked by the nexus group to consider raising the incentive amount or making ASHAs regular salaried employees and consider the possibility of providing them with health insurance. The availability of flexible funds with ASHAs was considered useful for hiring vehicles at odd hours for the transport of sick children and pregnant women when ambulance services were not available. Another significant intervention proposed was increased male engagement in community meetings through village fora like VHND/VHSNC. These fora could help negotiate and reduce social discrimination and also strengthen social accountability (Figure 4).

Discussion

The study adds to the existing knowledge that societal issues and personal challenges for ASHAs at their home and community fronts are among the more important barriers/challenges that prevented them from completing home visits and associated tasks with quality. The other reasons for incomplete age-appropriate home visits included gaps in the monitoring of ASHA's performance and mentoring system. Almost half of the ASHAs also accepted their lack of confidence in technical knowledge and communication skills. These factors shook community confidence in her capabilities and the importance given to her advice. The field-level staff including the ANMs, AWWs, block mobilizers, and ASHA supervisors strongly endorsed ASHAs viewpoint with particular emphasis on their social and domestic challenges, and importantly these were often overlooked. Mothers, even those never visited by ASHAs at home, felt that, ASHAs also lacked planning skills and consequently did not get the desired support from families for optimum performance.

The interconnectedness and complexity of the challenges in different sectors and aspects of human ecosystem have led to the recognition of the importance of transformative approaches in addressing and achieving sustainability (35). Nexus thinking and scenario planning have changed the way of doing things from linear to integrated and from monocentric to polycentric approaches (36). The novelty of the study is that it provides evidence of the interrelatedness of the multitude of barriers/challenges faced by the ASHAS along with solutions falling under the five nexus framework domains.

NPMs unambiguously recommended managing all the domains synchronously if the ASHA performance was to improve. The study data recommended interventions at the communication, organizational and educational levels to improve the quality of visits through enhanced skills and confidence of the ASHAs. This would necessitate reengineered training and follow up mentoring methods to enhance her credibility and respect in the community and abate to a certain extent the social and religious prejudices against the ASHAs. The social and family commitments of the ASHAs are important and complex challenges and need to be handled through engagement with the community at different levels e.g., Panchayati Raj members and the participation of men and elderly women in their families to help in negotiating ASHA's usefulness to the community with reduction of social discrimination; and enhancing her stature and respect in the community through reinforcement of her technical and communication skills. Incentives alone are insufficient to motivate the ASHAs for better performance as was done for HBNC Plus program. Timely release of due remuneration can be additional factors for motivating the ASHAs and soliciting their family support. The primary focus and responsibility of ASHAs can be better defined: if it remains maternal and child health activities, regular feedback, and monitoring will make them feel more responsible as well as accountable for different components of maternal and child health services.

The majority of the ASHAs in the current study perceived conflict between their domestic and professional responsibilities. Several previous studies have also shown that the personal needs and family commitments of community health workers interfered with their ability to make home visitations regularly and at times convenient to the beneficiaries (37–39). During the NPMs, the participants informed that the credibility and respect for the ASHAs particularly those from lower caste improved, and discrimination was less likely if they were technically competent, were not vague in their advice, and had good communication skills to impart messages with confidence and conviction.

The ASHAs have to navigate societal and cultural prejudices during their fieldwork (38) and household visits beyond their own "beradari" (caste/tribe/community group) were either not appreciated or trusted (40, 41). Another study reported maximum odds of getting ASHA's services if she belonged to a lower caste as she did not hesitate to visit a household from any community. In the present study, the reluctance to visit low caste households was more among the ASHAs from a higher caste (42). Communities are likely to trust their health workers if they are seen as part of the same community and background (43–46). The trust deficit compounded if ASHA's competence is suspected (47). Probandri et al. observed traditional practices related to the care of the new mother-child dyads also influenced the utilization of postpartum care advice and services. The social architecture further reinforced such practices when the mothers or mothers-in-law, members of the extended families, neighbors, and communities lived in the same or adjoining houses (48).

Mentoring and hand-holding emerged as important tools for the ASHAs' performance and quality of home visitations in several studies. Gilson et al. reported that high-quality supervision helped in the restoration and sustenance of trust of the community in the health system and its services (49). In a study from Ghana, 81% of the midwives had not been visited by their supervisors in time (50). Lack of supervision led to poor technical skills (51), stock-outs, and problems arising out of human resource deficit (52). The other reasons for the poor quality of home visitations were: inconsistent and non-reliable health messages, 'always in hurry' attitude of the health worker during home visits, difficulty in contacting them when in need, non-provision of relevant health education materials, non-adherence to follow-up schedule (53, 54), and unwelcoming attitude toward the ASHAs by family members (55). Nammazi et al. found that knowledge of new born danger signs rapidly declined from 85.5 to 58.9% 1-year post-training and the main predictors of retention of community health worker knowledge were age ($\geq$35 years) and post-primary level of education (56). The final NPM consultation observed that with the low level of education and social status in the community, current training formats were not suited for the ASHAs to acquire an adequate understanding of the complexity of the subject matter, and their subsequent translation in actual conditions. The group strongly recommended the need for re-engineering of training curricula, with a strong focus on technical skill building, developing self-assurance, and contextually understandable communication skills. Similar concerns and recommendations were reported in several other studies as well (57–60).

Complex interconnected challenges when addressed singly, at times may reduce one problem while exacerbating others. Studies have shown that tackling the challenges piecemeal has not helped to improve the ASHA's performance (61, 62). In a recent implementation study, the performance of ASHAs for home visitation and identification of sick young didn't improve significantly despite efforts by district health authorities to improve skill and technical competence (63). In a study by Creanga et al. (64) the mothers avoided accepting services from the ASHAs who couldn't deliver satisfactory quality postnatal home visitation despite having undergone training due to poor communication skills (64). Our study indicated that timely disbursement of incentives not only helped maintain their morale and motivation but also sent a positive message about their worth to their own families. Several studies have demonstrated a strong association between financial incentives and ASHAs performance (65, 66). Lewis and Bahety et al. also reported that low and delayed incentives were considered a major barrier to the service delivery by the ASHAs (67).

This study has some limitations. We applied NPF as a co-creation exercise involving a wide range of stakeholders and sectors for inductively developing a comprehensive understanding of the factors affecting home visitations by the ASHA, and the interrelatedness between barriers and potential solutions. We modified the broad principles of nexus planning for health system strengthening and improving the performance of frontline workers in resource constraint environments which also have deeply entrenched social, cultural, and other contextual factors. The rationale of giving importance and hearing to all the sub-group stakeholders/constituencies separately brought out several items and matters which required joint discussion to arrive at a mutually acceptable way forward. The challenges faced by ASHAs from forward and backward communities were different and had to be handled in a manner that required suggestions from both sides. The nexus approach guided us to identify and pursue synergies between health and non-health sectors i.e., Panchayati Raj [local self-government] recognizing their significant function and responsibilities to iron out some of the socio-cultural and economic biases operating at the village level. The feasibility and widespread applicability of NPF can be a concern. As mentioned above, successful NPF processes are dependent on identifying the sub-groups and sub-constituencies strategically for a series of group meetings/consultations. This will require deep insight into the local cultural, social, economic and, organizational milieu. Notwithstanding these limitations, the nexus framework did provide robust findings which can be triangulated with several published studies albeit done in a piecemeal manner from India and other low and middle- income countries (LMIC) settings. NPF has been successfully applied in environment, urban development, scrum methodology, water-energy-food (WEF) nexus approach in the MENA (Middle East and North Africa) countries, and many other areas for achieving sustainable development goals (SDGs) with sector-specific modifications (68). NPF offers a comprehensive structure for future researchers and implementation scientists to unravel the complexity and layers of health ecosystems and pursue efforts to improve the performance of community health workers. Research is also required to further refine NPF for wider application but its core philosophy should remain intact. Another limitation of the study can be the applicability of the findings from Raisen district to other parts of the state and country and other LMICs. The health indicators particularly related to tasks executed by ASHAs, Raisen falls in the lower one-third of the ranking of the Indian district (26). However, context and geography will continue to influence the relative significance of each of the five nexus domains.

In conclusion, the present study took a 360-degree view of the factors impacting the home visitation and related performance of the ASHAs and nexus planning groups emphatically recommended that each factor had an effect on or was dependent on the other factors and hence the remedies should include a more comprehensive approach rather trying for piecemeal solutions. The study showed that barriers and challenges of ASHAs can be classified under five broad domains. NPF stressed the imperative of approaching these barriers as interlinked challenges and resolution of any one component alone would not facilitate positive change. Future research and implementation agenda roadmap should include simultaneous interventions to improve the technical and communication skills to build the confidence of the ASHAs through reengineered training and follow-up mentoring methods; which is likely to enhance her credibility and respect in the community and abate a certain extent the social and religious prejudices against her. The social and family commitments of the ASHAs are important and complex challenges and need to be handled through engagement with the community at different levels. Another useful research agenda can be to determine the applicability of NPF in diverse settings and health system challenges.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics approval was obtained from the independent Ethics Committee of the INCLEN Trust International, New Delhi [DCGI reg no: ECR/109/Indt/DL/2014/RR-17]. Written informed consent to participate in this study was provided by the participants. Informant identity during the data analysis was kept anonymized. Verbal consent was taken from community representative and individual to participate in the nexus group meeting.

Author contributions

NA designed the study. Data curation was done by VD, SJ, AP, RD, SC, KG, SB, BH, MD, RM, RS, and PS. Data analysis was done by NA, VD, SJ, AP, RD, and SC. NA, VD, and SJ prepared the first version of the manuscript. All authors provided comments on subsequent drafts and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Caregiver distress: A mixed methods evaluation of the mental health burden of caring for children with bladder exstrophy

Katelyn A. Spencer[1†], Jaishri Ramji[2†], Pooja Unadkat[1], Iqra Nadeem[1], Parth A. Lalakia[1], Jay Shah[1], Pramod P. Reddy[3], Douglas A. Canning[1], Joao Pippi-Salle[4], Paul Merguerian[5], Anjana Kundu[6], Dana A. Weiss[1], Aseem R. Shukla[1], Rakesh Joshi[2] and Jennifer R. Frazier[1]*

[1]Department of General Surgery, Division of Urology, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [2]B. J. Medical College and Civil Hospital, Ahmedabad, India, [3]Department of Surgery, Division of Pediatric Urology, Cincinnati Children's Hospital, Cincinnati, OH, United States, [4]Sidra Medical and Research Center, Doha, Qatar, [5]Department of General Surgery, Division of Urology, Seattle Children's Hospital, Seattle, WA, United States, [6]Department of Anesthesiology and Pain Medicine, University of Rochester, Rochester, NY, United States

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EDITED BY
Britt Nakstad,
University of Botswana, Botswana

REVIEWED BY
Shuliweeh Alenezi,
King Saud University, Saudi Arabia
Yogesh Kumar Sarin,
University of Delhi, India

*CORRESPONDENCE
Jennifer R. Frazier
frazierj1@chop.edu

†These authors share first authorship

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Introduction: Caring for children with bladder exstrophy-epispadias complex (BEEC) exacts a long-term emotional toll on caregivers. Previous studies leave a gap in understanding the impact that caring for a child with BEEC has on caregivers in low- and middle-income countries (LMIC). We hypothesize that families and caregivers experience psychological distress that has long gone unaddressed.

Materials and methods: From 2018 to 2020, researchers conducted a multi-method evaluation of caregiver distress with participants recruited as part of the annual International Bladder Exstrophy Collaboration based in Ahmedabad, Gujarat, India. In 2018, pilot data was collected through cognitive interviews. In 2019, researchers conducted structured interviews predicated on themes from the previous year, which subsequently prompted formal mental health screenings in 2020. Caregivers who reported suicidal thoughts were immediately referred for intervention.

Results: In 2018, caregivers described the primary source of stigma arose from their village (n = 9, 26.5%). Caregivers also identified long-term concerns (n = 18, 52.9%), including future fertility and marital prospects, as sources of anxiety. In 2019, caregivers substantiated preliminary findings with the primary source of anticipated (n = 9, 31%) and experienced (n = 19, 65.5%) stigma again stemming from their communities. Both cohorts identified the collaboration as a positive source of support (n = 23, 36.5%). In 2020, caregivers stated decreased emotional wellbeing as number of subsequent repairs increased (n = 54, 75%, p = 0.002). Caregivers of children who underwent initial surgery within 5 years of screening reported higher anxiety (n = 46, 63.8%) and this was exacerbated as the number of subsequent repairs increased (p = 0.043).

Conclusion: Complex, long-term course of care, including additional surgeries, significantly impacts caregiver distress in the LMIC setting. Screening for caregivers of children with complex congenital anomalies, like BEEC, should be an essential element of any comprehensive effort to alleviate the global burden of disease.

KEYWORDS

bladder exstrophy-epispadias complex (BEEC), caregiver distress, quality of life, low- and middle-income countries (LMIC), stigma

Introduction

Similar to other children with significant anatomic defects, bladder exstrophy-epispadias complex (BEEC) patients are at a greater risk of psychosocial adjustment issues, including suicide ideation and behaviors (1), depression, and anxiety when compared to physically healthy children (2). The caregivers of these children also experience increased rates of stress that are comparable to the experiences of parents of children with other significant diagnoses, like type 1 diabetes (3). Specifically, BEEC and its associated incontinence causes stigma which can result in the isolation of a patient and their caregiver from family and community members (4). This increases the complexity of care that these patients need in order to achieve long-term wellbeing and maximize health-related quality of life.

The experienced and anticipated stigma (5) that these children and their caregivers can experience exists in all settings, but they are further complicated in low- and middle-income countries (LMICs) where 94% of congenital anomalies occur (6). Patients in these settings generally have less access to mental and physical health care (7). And, importantly for BEEC patients and caregivers, LMICs have less access to urinary absorptive clothing such as disposable diapers (4). Specifically, in India where the International Bladder Exstrophy Consortium operates, patients overwhelmingly live in close, multigenerational arrangements (8). This creates additional challenges for patients and their caregivers as the consequences of incontinence are amplified within close quarters.

The intensive surgical and medical management required to achieve anatomic integrity and future continence of children with BEEC may also be a contributing factor to caregiver and patient distress. The International Bladder Exstrophy Consortium (9), conceived in 2009 to partly address a large burden of unmet surgical need in India, utilizes the complete primary repair of exstrophy (CPRE) in an effort to minimize the number of subsequent repairs. But, the post-operative period can still be complicated by numerous events that could necessitate additional operations including penopubic fistula, bladder outlet obstruction, hypospadiac meatus at closure, and bladder dehiscence. These complications and the necessity for future operations are also impacted by the age at presentation for surgery and whether the patient requires a primary or redo repair after a failed initial closure at another location. We hypothesize that caregivers of BEEC patients will identify themes of stress, anxiety, and stigma within their lives and that higher numbers of subsequent surgeries contribute to higher levels of caregiver distress and anxiety.

Materials and methods

A sustainable, long-term, and mutually beneficial collaboration between academic research centers from high income countries (HICs) and a tertiary hospital in Ahmedabad, Gujarat, India with appropriate capacity was created in 2009 to provide care for BEEC patients (9). Overtime, the collaboration has grown to include Cincinnati Children's Hospital, Children's Hospital of Philadelphia, Seattle Children's Hospital, surgeons from Sidra Medical Center in Doha, Qatar, and a pediatric anesthesiologist with specialization in pediatric pain management. The annual collaboration takes place at a government funded, public hospital that serves a geographic catchment area of 60 million people. The collaboration recalls all of the patients annually, in addition to new patients, to be evaluated by a team of surgeons that are consistent from year to year. At this time, progress studies, including urodynamic evaluation, cystogram, ultrasound, and DMSA scans are performed. Surgical and follow-up plans are made for all patients.

The increased importance of long-term wellbeing and the impact of stigma on health-related quality of life spurred the collaboration to begin evaluating more holistic measures of post-operative success to assess gaps of care within the program. From 2018 to 2020, researchers conducted a multi-method evaluation of caregiver distress with participants recruited from the annual surgical collaboration. Sampling of patients was performed using a convenience sample of all returning participants of the cohort. Data was collected throughout the collaboration as time allowed. Each instrument used was independently forward and reversed translated in two regional languages and reviewed by expert members of the research team to screen for translation errors. Participants were surveyed by a bicultural and bilingual interpreter independent of the surgical team. Surgical history was collected from the medical team. IRB approval was provided by the Institutional Ethics Committee of the Civil Hospital, Ahmedabad and BJ Medical College. Written informed consent to participate in this study was provided by the patient's caregiver and/or the participant's legal guardian/next of kin.

In 2018, researchers collected pilot data through cognitive interviews using two existing quality of life questionnaires as a guide when creating the interview instrument: The Pediatric Urinary Incontinence Quality of Life tool (10) and the Chronic Illness Anticipated Stigma Scale (5). Participants included caregivers and patients who were awaiting initial repair of BEEC or returning for their annual follow-up visit. Information documented included patient demographics, questions for doctors, and perceptions of stigma.

In 2019, researchers returned to the annual surgical collaboration to conduct more focused and structured interviews based on the themes that emerged from 2018. All interviews were conducted in Gujarati and Hindi, recorded, forward and reverse translated by two unique individuals, transcribed, coded, and analyzed using NVivo. Data analysis and collection followed a grounded theory through an iterative process (11). Codes and themes were inductively developed using descriptive and *in vivo* coding techniques. Descriptive coding summarizes the topic of a brief section of the interview while *in vivo* coding uses the actual language of the qualitative data to produce a code (12). The codes were used to analyze the data and extrapolate themes from the interviews. Before finalizing the codebook, subthemes were identified until code and meaning saturation was achieved. Code saturation describes when no new themes have been identified by participants, and meaning saturation is when no new dimensions of a theme have been identified by participants.

These structured interviews reinforced the pilot data and motivated researchers to conduct formal depression and anxiety screenings in 2020 using well-validated quantitative measures of mental health indicators and health related quality of life. Participants were administered the Beck Depression Inventory (13), Beck Anxiety Inventory (14), and RAND 36-item Health Survey (15) to evaluate distress. These inventories are well-validated measures that have test-retest reliability and are widely used to detect and assess the intensity of anxiety and depression in patient populations. The RAND 36-Item questionnaire was administered to 73 patients. This questionnaire is one of the most widely used health-related quality of life questionnaires, and it assesses physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional wellbeing, energy/fatigue, pain, and general health perceptions (15). Caregivers who reported suicidal thoughts were immediately referred to a visiting counselor. All data analysis was performed by IBM's SPSS 28.0.1.

Results

The findings of patient and caregiver interviews, including prominent themes and illustrative quotes, are presented in **Tables 1**, **2**, respectively. In 2018, 34 participants were interviewed. Caregivers reported protective factors against stigma and anxiety including living with supportive families (n = 28, 82.4%) and interacting with (n = 8, 23.5%) or anticipating cooperative school administrators and employers (n = 4, 11.8%). Families reported that the majority of experienced (n = 8, 23.5%) and anticipated (n = 1, 2.9%) stigma arises from their village. Over half (n = 18, 52.9%) of caregivers report anxiety around the post-operative experience including concerns about future continence (n = 14, 41.2%) and marital prospects (n = 6, 17.6%). However, families report that they have a positive outlook for the future (n = 16, 47.1%) and the collaboration has helped them create a network of support they do not encounter in their hometowns (n = 7, 20.6%). Additionally, almost half (n = 13, 38.2%) expressed a high degree of trust in the medical team.

In 2019, researchers returned to ask about specific themes that emerged the year prior. Interviewees (n = 29) echoed what was learned in the previous year regarding family, benefits of the collaboration, trust in the medical team, and their child's future. Support from family members was further explored and caregivers identified that the primary type of support received was emotional (n = 13, 44.8%) Over half (n = 19, 65.5%) reported experiencing stigma and a third (n = 9, 31%) reported anticipating stigma from their communities. Many families expressed hope for their child's future (n = 12, 41.4%), but also worried about their child's ability to get married (n = 19, 65.5%), have children (n = 16, 55.2%), achieve independence (n = 7, 24.1%), and obtain complete continence (n = 14, 48.3%).

In 2020, researchers surveyed 72 caregivers of children who underwent surgical repair for BEEC. Descriptive information of the cohort is presented in **Table 3**. Forty-five (62.5%) reported moderate to severe depressive symptoms. Fifteen (20.8%) were referred immediately for counseling due to symptoms of depression and self-reported history of suicidality. Report of emotional wellbeing decreased as number of subsequent repairs increased (p = 0.002) for children who underwent primary repair for BEEC (54, 75%). Mean time since first repair for BEEC was 4.6 years. Of those with 5 years or less time since surgery (46, 63.8%), caregivers reported higher anxiety as number of subsequent repairs increased (p = 0.043).

TABLE 1 Qualitative interview themes.

Themes	Total		2018 Cohort (n = 34)		2019 Cohort (n = 29)	
Classmates and friends						
Anticipated stigma	13	21%	3	8.8%	10	34.5%
Experienced stigma	8	13%	4	11.8%	4	13.8%
Anticipated support	4	6%	2	5.9%	2	6.9%
Experienced support	9	14%	2	5.9%	7	24.1%
Collaboration benefits						
Found support and friends	23	37%	7	20.6%	16	55.2%
Gained perspective	11	17%			11	37.9%
Trust the doctors	25	40%	13	38.2%	12	41.4%
Family						
Anticipated stigma	5	8%	2	5.9%	3	10.3%
Experienced stigma	22	35%	10	29.4%	12	41.4%
Anticipated support	0	0%				
Experienced support	44	70%	28	82.4%	16	55.2%
Emotional	13	21%			13	44.8%
Financial	3	5%			3	10.3%
Physical	8	13%			8	27.6%
Future concerns						
Future fertility	18	29%	2	5.9%	16	55.2%
Ability to be independent	7	11%			7	24.1%
Future continence	28	44%	14	41.2%	14	48.3%
General quality of life	10	16%			10	34.5%
Marital prospects	25	40%	6	17.6%	19	65.5%
None	7	11%			7	24.1%
Genital cosmesis	4	6%	3	8.8%	1	3.4%
Positive outlook	28	44%	16	47.1%	12	41.4%
School administrators and bosses						
Anticipated stigma	4	6%	1	2.9%	3	10.3%
Experienced stigma	5	8%	1	2.9%	4	13.8%
Anticipated support	10	16%	4	11.8%	6	20.7%
Experienced support	17	27%	8	23.5%	9	31.0%
Surrounding community						
Anticipated stigma	10	16%	1	2.9%	9	31.0%
Experienced stigma	27	43%	8	23.5%	19	65.5%
Anticipated support	1	2%	1	2.9%		
Experienced support	12	19%	3	8.8%	9	31.0%

Discussion

This study is the first of its kind to assess the impact of BEEC caregiver distress among LMICs, and more specifically, Indian families. The findings are consistent with previous work on caregiver distress in parents of BEEC children in HICs. Mednick et al. found in a cohort of American caregivers of children with BEEC that their level and frequency of stress was comparable with that of parents of children with type 1 diabetes (3). Specifically, these parents were concerned with the long-term impacts of BEEC on their children, including helping with hygiene and uncertainty about the future. These themes are congruent with the themes identified from Indian parents and caregivers who had anxiety about the post-operative experience.

TABLE 2 Illustrative quotes from patients and caregivers.

Community	
"A lot of families say that they don't like "the urinating child," so we hesitate to take our child anywhere. Whenever our child goes to their house and sits on their couch, they get disgusted and become hesitant towards him sitting there."	
"We got our daughter engaged. The in-laws would come visit our house often and one time we visited their house as well. My child was playing around and sat down on the mattress and urinated on it. My daughter's to-be mother-in-law said really mean and bad words to us because of that. I got really emotional because my daughter's engagement got broken off because of that."	
"We are working so hard for her right now that our daughter becomes normal just like other children. We don't want her to feel any shame from the society."	
"They call her "dirty [patient name]". They kept saying that she smells bad and wouldn't let her play with other kids. They also told me, what kind of daughter have you given birth to, telling me that I have done bad things in life and this is the result of that."	
"People do talk about whether she will be able to get married when she grows up and also question what we will do if her urine leakage won't stop. All the community members say this on my face and behind my back as her condition is very obvious and right in front of us."	
"The community members don't say anything to our faces, however, they do talk behind our back. Others have told us that community members still talk about his conditions in our absence. We feel bad about their talks, however, we can't do anything about it so we just ignore them."	
Future concerns	**Classmates**
'We are not worried about anything right now. After Dr. Reddy's presentation, I am not that concerned about his condition or future anymore. Before that we were worried about marriage and having kids in the future after all the surgeries get done. No, I don't have any questions right now."	"However, the children at school do tease him by calling him names. People in the neighborhood also tease him, and he comes home crying. His mom gets frustrated and goes to fight with their mothers. This causes disturbance and arguments with our neighbors."
"We also worry and hope that she won't take any bad steps of harming herself because of her physical condition. We worry that in the future some other women in the future will tease her that her body looks different than theirs."	"The most worrisome aspect of school is the friends at school who tease him because of the urine smell. My child comes home crying complaining to us that other kids were teasing him because of the smell."
Family	**Collaboration benefits**
"Our family said what was the point of raising such a child. After being married for 10 years, we finally got a child and we will surely take care of him. On seeing his condition, I don't have anything to say but we won't give up on him even though my family members have not been supportive."	"It has been a wonderful experience at the camp. We made a whole group of parents who have been coming here for many years now. We all get together in January and even in between sometimes. The kids play together, and we also spend time chatting."
"When she was born, all the family members said that your daughter should just be killed because of her condition. They told us that we should poison her because of her condition."	"I have been coming for 12 years now and there hasn't been a time when I have missed being here for the camp since then."
"Yes, our family was very supportive. They said to go get this treatment done and not to worry about anything at home when we were gone as they would handle everything at home for us."	"Yes, we do feel like family here. We feel thankful that the doctors have been helpful in getting our child better. Other family members are like our close relatives now as we have been coming here for 4 years."
"My family has been very supportive as they are very open-minded people. We live in a joint family with total of 9 members. We sometimes don't even have to take care of the child as everyone at home takes care of him."	"We felt more relieved after seeing other girls have the same condition. We felt more relieved that my child isn't the only that is going to such a rare condition."
	"We provide encouragement to the parents, especially to the new ones at the camp."

The Indian parents were most concerned about their child's ability to get married, have children, achieve independence, and obtain complete continence.

The India cohort does differ substantially from the studied HIC families in terms of average socioeconomic status and cultural factors that include multigenerational housing and general access to mental health services. These factors contribute to the added familial and community-based sources of anticipated and experienced stigma that the India cohort identified. Specifically, the parents at Civil Hospital spoke about stigma that arose from their villages and classmates at school with support coming from their families and school administrators and employers. Despite these differences, both sets of families had similar primary concerns surrounding overall emotional and physical wellbeing of their children, and this goes to show that parents around the world have the same anxieties about their children when they are born with congenital urological anomalies.

The high levels of caregiver distress that was elucidated from the 2020 mental health instruments is also consistent with the documented higher risk of depression, anxiety, and suicidality that has been reported in studies on the long-term wellbeing of patients with BEEC (16–19). While these studies focused on patients themselves, the effects of BEEC on parental and caregiver wellbeing are equally drastic and important. Additionally, subsequent surgeries were found to increase the risk of emotional distress for caregivers of children with BEEC, and this was exacerbated when patients and caregivers were within 5 years of their initial operation. With recall bias in mind, this effect could also speak to the diminished stress around medical procedures as patients and caregivers have become accustomed to them overtime and as expectations for families are repeatedly set by physicians and the care team.

Recommendations

With these considerations in mind, future efforts should be made to continue to address the emotional wellbeing and mental health of BEEC patients and caregivers to maximize

TABLE 3 Cohort characteristics and mental health indicators.

Characteristics		Total cohort ($n = 72$)
Age at surgery, m		
Median (25th to 75th percentiles)		20 11–50
Sex, No. (%)		
Male		58 80.56%
Female		14 19.44%
Time since first repair, y		
Avg. (St. Dev.)		4.6 2.78
Diagnosis, No. (%)		
Primary bladder exstrophy		45 26.63%
Redo bladder exstrophy		13 7.69%
Primary penopubic epispadias		12 7.10%
Redo penopubic epispadias		2 1.18%
Beck inventory (ranges from 0 to 63)		
Depression inventory summary score		
0–10	Normal	24 33.33%
11–16	Mild mood disturbance	16 22.22%
17–20	Borderline clinical depression	10 13.89%
21–30	Moderate depression	12 16.67%
31–40	Severe depression	9 12.50%
40+	Extreme depression	1 1.39%
Anxiety inventory summary score		
0–7	Minimal anxiety	40 55.56%
8–15	Mild anxiety	15 20.83%
16–25	Moderate anxiety	15 20.83%
26–63	Severe anxiety	2 2.78%
RAND 36-Item Mental Health Indicators (ranges from 0 to 100)		
Emotional wellbeing average, Avg. (St. Dev.)		64.67 23.43

overall quality of life for this population. It is important to continue to reduce the need for subsequent surgeries by promoting early and primary referrals as opposed to later and after an initial failed closure at another location. Additionally, continuing to focus on and improve post-operative care of these patients in order to prevent complications that would require subsequent procedures should be made a priority. This is all in addition to the need for robust mental health services for this population to prevent the negative ramifications that accompany caregiver and patient distress. It is well documented that BEEC patients experience higher rates of depression, anxiety, and suicidality than their physically healthy peers (1, 16–19), and any efforts that can be made to reduce this would be beneficial to the long-term wellbeing of these patients. And, now that it is known how high the levels of depression and anxiety are among caregivers of BEEC patients, these same services should be applied to them as well.

In order to achieve this, support of all kinds should be increased for the LMIC BEEC patient and caregiver population. The resource scarcity for BEEC compared to other chronic medical conditions and congenital anomalies is a result of the relative rareness of the condition, but these services are still essential for this population. We are grateful that the Government of Gujarat in India is investing in the infrastructure of Civil Hospital in Ahmedabad and providing funding for the free care of BEEC patients and their caregivers. Still, due to the inherent economic challenges of families treated in LMIC settings, the collaboration continues to solicit support to provide necessary support to families seeking care and strengthening the capacity of Civil Hospital to provide them.

While families at the collaboration are incredibly thankful for the surgical care they receive and there have been numerous improvements seen, we acknowledge that there is more work that could be done to improve the long-term holistic wellbeing of BEEC patients in India. The stigma and anxiety experienced by BEEC patients and their caregivers within India requires more specialized and tailored care in addition to the surgical achievement of anatomical and functional integrity. As a result, the inclusion of long-term wellbeing and quality of life should be included as a metric of post-operative success in both HICs and LMICs. This necessitates the inclusion of efforts to continue to reduce the need for subsequent operations in addition to a robust mental health program for patients and caregivers within the delivery of care to better serve this unique patient populations' needs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the Civil Hospital, Ahmedabad, and B. J. Medical College. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

JF: full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JR, PR, DC, JP-S, PM, AK, DW, AS, RJ, and JF: concept and design and critical revision of the manuscript for important intellectual content. KS, JR, PU, IN, PL, JS, DW, AS, RJ, and JF: acquisition, analysis, and interpretation of data. KS, DW, AS, and JF: drafting of the manuscript. KS and JF: statistical analysis. DC and AS: obtain funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Britt Nakstad,
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REVIEWED BY
Olugbenga A. Mokuolu,
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Muhimbili National Hospital, Tanzania
Daynia Ballot,
University of the Witwatersrand, South Africa
Clement Ezechukwu,
Nnamdi Azikiwe University, Nigeria

*CORRESPONDENCE
Vinay Kampalath,
kampalathv@chop.edu

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The delivery of essential newborn care in conflict settings: A systematic review

Vinay Kampalath[1,2,3,4]*, Sarah MacLean[5], Abrar AlAbdulhadi[5] and Morgan Congdon[2,4,6]

[1]Division of Emergency Medicine, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [2]Center for Global Health, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [3]London School of Hygiene and Tropical Medicine, University of London, London, United Kingdom, [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [5]Division of General Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [6]Section of Hospital Medicine, Division of General Pediatrics, Department of Pediatrics, Global Children's Hospital of Philadelphia, Philadelphia, PA, United States

Introduction: Although progress has been made over the past 30 years to decrease neonatal mortality rates, reductions have been uneven. Globally, the highest neonatal mortality rates are concentrated in countries chronically affected by conflict. Essential newborn care (ENC), which comprises critical therapeutic interventions for every newborn, such as thermal care, initiation of breathing, feeding support, and infection prevention, is an important strategy to decrease neonatal mortality in humanitarian settings. We sought to understand the barriers to and facilitators of ENC delivery in conflict settings.
Methods: We systematically searched Ovid/MEDLINE, Embase, CINAHL, and Cochrane databases using terms related to conflict, newborns, and health care delivery. We also reviewed grey literature from the Healthy Newborn Network and several international non-governmental organization databases. We included original research on conflict-affected populations that primarily focused on ENC delivery. Study characteristics were extracted and descriptively analyzed, and quality assessments were performed.
Results: A total of 1,533 abstracts were screened, and ten publications met the criteria for final full-text review. Several barriers emerged from the reviewed studies and were subdivided by barrier level: patient, staff, facility, and humanitarian setting. Patients faced obstacles related to transportation, cost, and access, and mothers had poor knowledge of newborn danger signs. There were difficulties related to training and retaining staff. Facilities lacked supplies, protocols, and data collection strategies.
Conclusions: Strategies for improved ENC implementation include maternal and provider education and increasing facility readiness through upgrades in infrastructure, guidelines, and health information systems. Community-based approaches may also play a vital role in strengthening ENC.

KEYWORDS
pediatrics, neonatal, humanitarian, refugee, perinatal mortality, global health, conflict

Introduction

Recent humanitarian crises in Ethiopia, Afghanistan, Syria, Yemen, and Ukraine have focused international attention on the health impacts of armed conflicts. In these contexts, children are especially vulnerable. In 2021, the United Nations High Commissioner on Refugees estimated that of the unprecedented 84 million forcibly displaced people worldwide, 42% (or 35 million) were children (1). Of all children, newborns are among the most vulnerable; since 2018, at least one million babies have been born into refugee status (1).

Over the last 30 years, global reductions in neonatal mortality (defined as deaths within the first 28 days of life) have not been as dramatic as reductions in mortality among children under five years of age (under-5s) (2). Currently, at least 60 countries are estimated to miss the Sustainable Development Goal of a neonatal mortality rate of under 12 deaths per 1,000 live births by 2030 (3). Geographically, the pattern of neonatal mortality is uneven, with higher neonatal mortality rates occurring in conflict-affected countries (4). Increasingly, global neonatal mortality is concentrated in countries affected by conflict and displacement, such that of the 15 countries with the highest neonatal mortality rates in the world in 2015, 14 were experiencing conflict and displacement at the time (5, 6). For example, while global neonatal deaths account for 38% of all under-5 deaths, in some conflict settings, such as Myanmar and Yemen, that number has increased to 53% (7, 8).

As a result of these disparities, attention has turned to reduce neonatal mortality in humanitarian crises. One such effort is the Newborn Health in Humanitarian Settings: Field Guide, developed by the Inter-Agency Working Group on Reproductive Health in Crises (7). Developed in 2017, the Field Guide provides guidelines designed to reduce neonatal mortality in humanitarian settings. It describes essential newborn care (ENC) as a set of fundamental services for every newborn. ENC includes thermal care, initiation of breathing, feeding support, and infection prevention. ENC also describes several preventive and promotive health actions, including the identification of neonates in need of advanced care, the dispensation of anticipatory guidance to families, and postnatal checks during the first month of life (7). The Field Guide also details interventions for babies born prematurely or with low birth weight, babies with suspected serious bacterial infections, and babies with a history of intrapartum complications. The Field Guide organizes recommendations at three service delivery levels: the household, primary care facility, and hospital. In this systematic review, we sought to understand the barriers to and facilitators of ENC implementation in humanitarian settings, particularly at the facility and hospital levels.

Methods

The search strategy was designed by all study authors. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9). Articles were accepted for screening only if they included search terms from each of three separate concepts: (a) the conflict setting, (b) newborns, and (c) ENC. The full syntax for the systematic search strategy was informed by previous systematic reviews that focused on health in humanitarian crises and is available in **Supplementary Appendix S1** (10, 11). Two librarians were consulted to review the syntax.

All identified citations were uploaded into Covidence, a systematic review management platform. Duplicates were removed automatically by Covidence and a standard abstract screening process was applied. Two reviewers (AA, SM) independently screened each abstract for relevance to the subject matter. All studies considered eligible for full-text review by both reviewers were automatically included, and disagreements were resolved by consensus with a third reviewer (MC or VK). Each full-text manuscript was assessed for eligibility by two reviewers, and disagreements were again resolved by consensus with a third reviewer. Grey literature was reviewed similarly. Two authors (MC, VK) hand-searched included articles' reference lists to determine additional eligible articles. The manuscripts deemed eligible for final inclusion underwent data extraction by two reviewers to identify the study design, methods, aims, and findings. The team evaluated data extraction results to achieve consensus. The PRISMA flowchart, which details this search strategy, can be found in **Figure 1**.

We searched published literature in English from the beginning of November 2017, the date that the Field Guide was published, through September 28, 2021. Peer-reviewed literature was searched using CABI Global Health, Excerpta Medica Database (Embase), Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Database of Systematic Reviews. We searched for grey literature in databases from the Healthy Newborn Network, International Rescue Committee, International Committee of the Red Cross, Médecins Sans Frontières (Epicentre and Field Research), Save the Children, and UNICEF. Reference lists from retrieved articles were screened for relevant studies.

For this review, a humanitarian crisis was defined as a circumstance in which civilian mortality was significantly and persistently above a population's baseline, such that there was severe disruption to society, and there was a requirement for support from national, international, and multilateral partners (10, 12). Internationally accepted definitions of refugees and internally displaced people (IDPs) were utilized in referring to affected populations (13).

Eligibility criteria

Our target population included neonates, defined as infants in the first 28 days of life. We excluded resettled refugee populations. Eligible publications included a description of ENC in a conflict setting, with a description

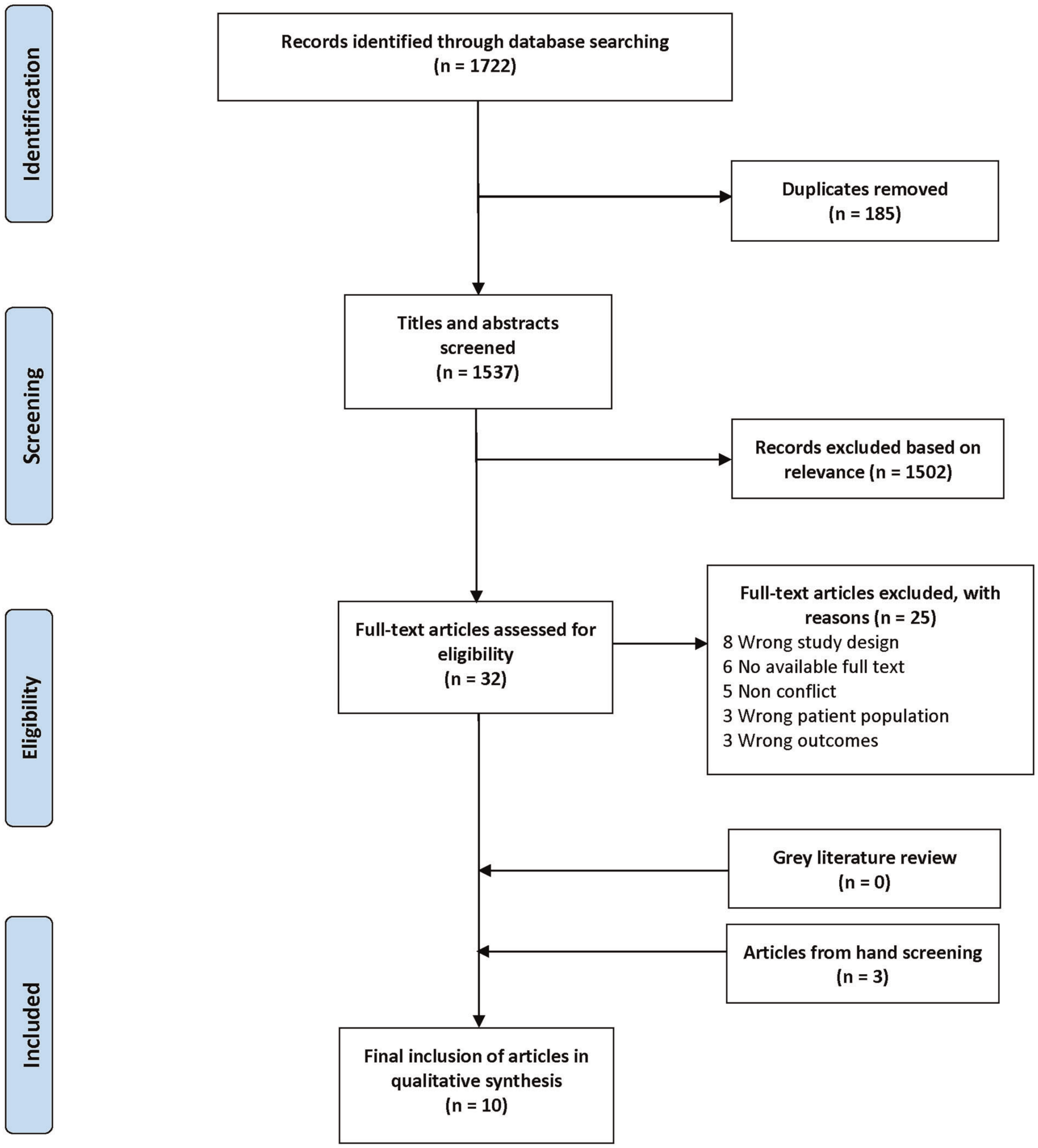

FIGURE 1
Flowchart of database search results and record screening.

of barriers or facilitators. Our search focused on interventions targeting the newborn, so we excluded literature that focused on the antenatal period. We excluded case reports, editorials, rapid assessments, and non-scientific reports. We applied the same inclusion criteria for indexed grey literature. The complete list of inclusion and exclusion criteria is found in **Table 1**.

Quality assessment

The quality of included studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (14). Each full-text article received quality assessment by two reviewers, and discrepancies were resolved through group consensus. Studies

TABLE 1 Inclusion and exclusion criteria for systematic review.

Subject	Inclusion criteria	Exclusion criteria
Populations	- Refugees, IDPs, and other populations affected by conflict - Neonates (defined as infants in the first 28 days of life)	- All other children (e.g., resettled refugees) - Children aged 29 days of life and greater (NB: Articles that discuss infants up to two months of age will be included if they are grouped with neonates aged day 0–28.)
Outcomes	- Delivery of ENC, with a focus on barriers and facilitators	- Any other outcome - ENC components exclusively related to antenatal period
Study designs	- Primary research of any quantitative or qualitative study design from academic and grey literature that describes an ENC intervention and its delivery	- Case series/reports, rapid assessments, field assessments, non-scientific reports
Language	- English	- Any other language
Dates	- Publish dates spanning 1 November 2017 to 28 September 2021 (date that review was conducted), inclusive	- Publish dates 31 October 2017 and earlier

were awarded one point for each item of the 22-point STROBE checklist. The total points awarded to each study were divided by the total possible points to obtain a percentage score. Studies were defined as low, moderate, and high quality with scores of <33%, 33%–66%, and >66%, respectively.

Results

Ten articles were included for final review. The details of these studies are found in **Table 2**. Notably, none of the 572 screened grey literature records met the eligibility criteria for final inclusion. The ten articles represent nine countries [Afghanistan, Cameroon, Chad, the Democratic Republic of Congo (DRC), Niger, Somalia, South Sudan, Uganda, and Yemen]. The barriers and facilitators that emerged from this systematic review were subdivided by level (patient, staff, facility, and humanitarian setting). Some factors are cross-cutting and appear at multiple levels.

Patient-related factors

There were several patient-level barriers to ENC delivery. A case study in Yemen reported on factors that impeded patient access to facility care, such as geographical constraints, roadside checkpoints, and transportation (15). Yemeni women, who were noted to traditionally prefer home births, would only seek facility-based care when experiencing complications due to difficulties related to access. In a study from the DRC, 80% of women arriving at emergency obstetric and neonatal care (EmONC) facilities traveled by foot, some for up to two days (16). Transportation was also an impediment when newborns required referral for intensive care (17). As Eze, et al. reported, over two-thirds of newborns in northwestern Yemen traveled for over an hour for transfer. Tappis, et al. reported that other demand-side factors, such as distrust in health providers and reprioritization of needs, contributed to decreased acceptability of certain preventive services, including immunization (15). Two studies also reported that costs related to transportation and medications were distinct barriers for patients (15, 18).

A key element of postnatal ENC includes counseling families on recognizing newborn danger signs, so that they seek care for unwell babies. In several studies, low maternal knowledge of these warning signs, hygienic cord care, and breastfeeding reflected inadequate ENC delivery (19–21). In one survey of four health facilities in Somalia, only 40% of mothers received pre-discharge education on ENC due to the short length of stay after childbirth and inadequate staff training (21). In a descriptive study evaluating newborn care in South Sudan, maternal knowledge of newborn danger signs was suboptimal; only 20% of mothers could identify four or more danger signs (20). In a quasi-experimental study in Somalia that evaluated the introduction of an intervention based on the Field Guide, pre-discharge education for mothers on breastfeeding and newborn danger signs had no significant improvement following the intervention, highlighting the challenge to achieving meaningful gains in maternal education (22).

Staff-related factors

Some of the variability in implementation of ENC was partly due to variation in staff skill level (21, 23). A study in displacement camps in South Sudan found that newborns delivered by skilled birth attendants (SBAs) were more likely

TABLE 2 Overview of included studies with study characteristics and summaries of key findings.

First author	Study setting and year	Participants and sample size	Summary of findings
Amsalu 2019	Four PHC facilities in Somalia (2016)	253 women, aged 15–49 years old, who delivered at PHC facilities	- The majority of childbirths were attended by skilled health workers, but quality of care varied - ENC interventions were not universally available - There was a low prevalence of handwashing, breastfeeding support, and skin to skin placement, but drying occurred
Amsalu 2020 (Somalia, Chad, Cameroon, Niger)	Healthcare facilities in conflict settings - Somalia (2016–2020), Chad, Cameroon, and Niger (2018–2019)	404 HCWs in conflict settings in Somalia, Chad, Cameroon, and Niger	- After Helping Babies Survive training, providers' knowledge improved and skills in newborn resuscitation improved (mean score difference +65.1%) - Learned skills were retained at the 18-month follow up - Low-dose, high-frequency trainings were effective in building competence - Lack of equipment made trainings difficult - Cross-functional trainee groups improved team dynamics
Amsalu 2020 (Somalia)	One healthcare facility in Somalia (2016–2018)	690 women, age 15–49 years, who sought childbirth care	- Intervention package (provider education, newborn supply provision, development of newborn registry) was feasible and effective in improving ENC at facility level - Knowledge and skills gained after training were mostly retained at the 18-month follow-up - Some aspects of ENC (handwashing, pre-discharge education) did not improve - Newborns receiving 2+ ENC practices improved from 19.9% at baseline to 94.7% at endline
Atiqzai	Public health facilities with at least 5 births per day on average in Afghanistan (2016)	Managers, SBAs, and mother-baby dyads at 226 public health facilities	- There was no specific pattern in availability of supplies and guidelines for ENC - SBA knowledge of ENC was slightly higher at district hospitals and PHC facilities compared with provincial, regional and specialty hospitals where the majority of facility births occur - There was inadequate knowledge of low-cost, high-impact ENC practices - There were inadequacies in pre-discharge examinations, postpartum counseling, postpartum care, warning about newborn danger signs
Eze	Single-center NICU in Yemen (2017–2018)	976 neonates (<29 days)	- Predictors of neonatal deaths were preterm birth, LBW, and traveling >60 min to NICU - Most common admission diagnoses were complications of prematurity (34.9%), perinatal asphyxia (34.4%), neonatal jaundice (18.8%), and neonatal sepsis (16.1%)
Hynes	Health facilities in DRC (2015–2016)	394 women aged >18 who underwent uncomplicated SVD	- Both the enhanced intervention group (receiving an additional QI methodology to test changes to care) and the control group showed improvements over time following clinical training on BEmONC, ENC, and partograph use - Enhanced intervention group showed a greater rate of change than the control group for AMTSL and ENC and achieved 100% ENC completion at endline
Komakech	Refugee settlements in one district of Uganda (2016)	Women, aged 18–49 years, who had delivered a baby in the last six months	- 57% of mothers breastfed their newborns within an hour, 50.1% cleaned their newborns' cord appropriately, 12.7% of newborns had a bath >24 h after birth, and 17% of newborns received optimal thermal care - Mothers aged 20–24 were less likely to perform good cord care - Mothers with the least primary education and those who identifed as Catholic were more likely to have initiated breastfeeding early
Mizerero	Public facilities in DRC (2006–2013)	Data on 35,283 deliveries	- No health centres could provide all basic EmONC services - Only 30% of the minimum acceptable number EmONC facilities was met - Resources needed for EmONC and institutional referral were scarce in surveyed health centers
Sami	Health facilities in displacement camps in South Sudan (2016)	343 mother-baby dyads and 13 midwife birth attendants who provided services	- Mothers' knowledge of danger signs was poor - Postnatal monitoring was inconsistently observed, but those babies delivered by SBAs (as opposed to TBAs) were more likely to receive postnatal monitoring

(*continued*)

TABLE 2 Continued

First author	Study setting and year	Participants and sample size	Summary of findings
			- Certain practices critical to ENC were less likely to be observed by unskilled birth attendants - Service availability and readiness for ENC was low at the facility level (electricity, supplies, staffing not adequately available) - Midwives spent most of their time on non-patient-contact activities
Tappis	Yemen (2015–2018)	National and sub-national government authorities, humanitarian agency staff, and HCWs (181 total)	- Service delivery and care-seeking patterns have been impacted by insecurity, reduced availability of health services, and economic downturn - The deterioration of government authority in Yemen has exacerbated humanitarian assistance and made governance difficult - Challenges to service delivery and intervention coverage included insecurity (attacks against healthcare specifically, stress among staff), politicization of aid (national, subnational, and non-state actors), health system capacity, and cost barriers to seeking care - Staff members were incentivized to leave Yemen or move from public to private clinics due to better pay

Abbreviations: AMTSL, active management of the third stage of labor; BEmONC, basic emergency obstetric and newborn care; DRC, Democratic Republic of Congo; ENC, essential newborn care; LBW, low birth weight; PHC, primary health care; NICU, neonatal intensive care unit; QI, quality improvement; SBA, skilled birth attendant; TBA, traditional birth attendant.

to receive postnatal monitoring compared to those delivered by traditional birth attendants (TBAs) (RR: 1.59, 95% CI: 1.09–2.32) (20). Observations of clinical practice in Afghan public hospitals demonstrated that high-impact, low-cost, and low-technology ENC actions, such as thermal care, delayed cord clamping, and breastfeeding promotion, were not routinely conducted (23). Pre-discharge counseling of mothers was also noted to be frequently omitted or insufficient in many studies (22–24).

Several reviewed records reported educational initiatives that successfully trained health care workers (HCWs) on ENC and improved newborn outcomes. A study in Somalia, for example, assessed the impact of an intervention package consisting of HCW training, distribution of newborn-specific

TABLE 3 Barriers to ENC delivery and strategies for improvement, by level.

Level	Barriers	Strategies for improvement
Patient	• Insufficient maternal knowledge of newborn danger signs • Transportation barriers (e.g., distance, security checkpoints) • Cost (e.g., referral, medicines)	• Initiatives designed to improve maternal education and build trust within communities • Community-based strategies (e.g., community midwives)
Staff	• Inadequately trained staff • Pay differentials between public sector and international NGOs • Time constraints from administrative duties and splitting time between clinical settings	• Dedicated trainings for HCWs • Mentorship by supervisors • Incentives such as promotion and pay-for-performance
Facility	• Variable service availability or coverage • Inadequate infrastructure and supplies • Lack of interfacility referral mechanisms	• Mother-baby-friendly spaces • Up-to-date clinical guidelines and standard operating procedures (SOPs) • Adoption of neonatal signal functions • Improvements in health information systems
Humanitarian setting	• Insecurity • Donor-driven prioritization • Breakdown in governance • Attacks against healthcare	• "Strategic" governance • Negotiated access to populations in need

commodities, and the development of a newborn register on three ENC behaviors (skin-to-skin contact, dry cord care, and early breastfeeding). Amsalu, et al. demonstrated that after the intervention was implemented, newborns were more likely to receive at least two (OR: 64.5, 95% CI: 15.8, 262.6, *P*-value <0.001) or all three (OR: 220.0, 95% CI: 33.7, 1443.0, *P*-value: <0.001) ENC interventions (22). Another study from the DRC showed that an experimental group receiving a participatory quality improvement initiative designed to improve facility-based maternal and neonatal care reached 100% ENC coverage at the end of the study period, with a greater rate of change in the uptake of ENC compared with the control group (OR: 49.62: 95%, CI: 2.79–888.28) (16). Other studies demonstrated that frequent refresher trainings and cascade training models aided in long-term knowledge retention and created an environment that maximized patient care and staff training, respectively (15, 24).

Retaining qualified HCWs in conflict settings was a recurrent barrier. HCWs reported being overworked. Midwives in Yemen were pulled into primary care practice in the community and had less time to devote to their EmONC activities (15). In South Sudan, midwives only spent 40% of their routine workday in direct patient care; the remaining 60% of their time was spent in non-patient-facing tasks such as documentation, meetings, supervision, and cleaning (20). Furthermore, pay differentials, particularly among international non-governmental organizations, private clinics, and public health centers, contributed to staff turnover. In Yemen, Tappis, et al. noted that harmonizing cross-sector financial and non-financial incentives would contribute to maintaining levels of providers for adequate care across the health system (15).

Facility-related factors

In the articles surveyed for this systematic review, many facilities had variable or low availability of ENC services (18, 20, 21). In some cases, not all facilities offered newborn services. In other settings, some facilities were closed. For example, less than 40% of EmONC facilities surveyed in the DRC provided services on an around-the-clock basis (18). Infrastructure and supply availability were repeatedly mentioned as significant factors affecting a facility's ability to deliver ENC (15, 18, 20, 23). In Yemen, clinics and supply warehouses had been destroyed or damaged by air strikes, shelling, and looting (15). Sami, et al. reported that in South Sudan, although all clinics had running water, two of the five facilities surveyed had no electricity for at least half of each month (20). Irregularity of supply chains produced insufficient medical goods for service demands. A cross-sectional quality assessment of public health facilities in Afghanistan demonstrated that only 53.8% of facilities had blankets or towels available for thermal care; all facilities lacked at least one item needed for neonatal resuscitation (23). A functioning suction device and appropriate-sized face mask were available in less than 75% of the facilities surveyed. Other studies in Cameroon, Chad, Niger, Somalia, and South Sudan reported similar supply shortages of critical medical commodities (20, 21, 24).

In addition to lacking material goods, facilities did not have functional processes in place to be ready for ENC. The lack of institutional guidelines for neonatal resuscitation and infection prevention in some settings was particularly notable. In Afghanistan, for example, only 48% of public sector hospitals surveyed had a protocol for ENC, and 44.7% had guidelines for emergency obstetric and newborn care (23). Another study found that the lack of appropriate escalation guidelines for neonates who do not adequately respond to the Helping Babies Breathe resuscitation algorithm created circumstances in which "resuscitation [was] conducted in an ad hoc manner" (24). The studies included in this systematic review also revealed that facilities had inadequate referral mechanisms, health information systems, newborn registries, and adherence to quality-related process indicators (15, 18, 22, 24).

Humanitarian crisis-related factors

Only one article from the Yemeni context described the contextual political, economic, and security barriers related to protracted humanitarian crises. There, two warring parties – the internationally recognized government and the de-facto authority – essentially acted as dueling coordinators of health system activities, leading to weakened authority, duplication of staff, confusion about service priorities, and erratic communication (15). In this study, Yemeni Ministry of Public Health and Population (MoPHP) officials reported feeling that their ability to manage programs and decide on health priorities was particularly hampered after the conflict escalated in 2015, a time when international agencies and donors became the principal decision-makers. MoPHP officials reported that external priorities, such as outbreak control and acute malnutrition care, drove resource allocation, whereas a fuller investment in health systems strengthening, infrastructure rebuilding, primary health care, and a wide array of reproductive, maternal, neonatal, child, and adolescent health services were not prioritized in all governorates (15). In this study, MoPHP respondents also reported the toll of insecurity on their work. Intimidation, injury, fear for family members, and acute and chronic stress were relevant barriers to MoPHP respondents' ability to carry out their work (15).

Quality assessment

All studies met the criteria for screening using the STROBE checklist, and all were found to be high quality. The STROBE assessment did identify areas of low-quality reporting for each study, however (10). Only seven studies described efforts to address potential sources of bias in relation to study results (16, 18–23). Two studies lacked a detailed description of their participants (or non-participants) at each stage of the study or to justify the final sample size (16, 24).

Discussion

The results of this systematic review reveal several obstacles to the delivery of ENC in humanitarian settings; our findings, described in **Table 3**, echo earlier studies that detail similar barriers. As geography may impose access constraints for patients, newborn care was noted to be less frequent in remote or out-of-camp settings (11, 25). Staff-related barriers were noted by many studies that cited high turnover, local insecurity, absenteeism, lack of female workers, and low salaries as critical factors that prevent retention (25–28). Having an inadequately trained cadre of staff is yet another barrier, as SBAs are not routinely present in conflict settings (25, 27, 29). Funding shortfalls have created facilities with poor infrastructure and insufficient newborn-specific supplies (25, 27). Health systems also face issues related to poor referral mechanisms, lack of standardized protocols, and inadequate health information systems (25, 26, 30). Barriers related to the overall ecosystem, such as political instability and the politicization of health, have been cited by other researchers, who note that even the most well-designed technical interventions can be imperiled in a humanitarian crisis (5, 6).

While the Field Guide provides several valuable clinical recommendations, it is critical to first identify high-impact, low-cost actions for all newborns that can potentially decrease mortality. The impact is potentially significant, as Bhutta, et al. estimated in 2014 that 420,000 lives could be saved by 2025 through improvements in ENC actions (31). Several studies have classified immediate ENC behaviors that fall into this category, such as the provision of thermal care and delayed bathing to prevent hypothermia, the promotion of exclusive breastfeeding within the first hour of life, vigorous stimulation of babies who are not spontaneously breathing, and the promotion of hygienic umbilical cord and skin care (31–33). Infection prevention measures at home and in a facility have also been demonstrated to decrease neonatal mortality (31). Other low-cost, promotive actions for healthy newborns include skin-to-skin contact, tetracycline ophthalmic ointment, intramuscular vitamin K prophylaxis, and weighing and registering the baby. Pre-discharge newborn examination and the concomitant provision of anticipatory guidance are simple and life-saving interventions that were not routinely performed in the records reviewed for this study (22–24). Many of these actions can occur at the community level and require minimal material or training inputs (33).

After considering which actions to target, it is important to consider how to best facilitate ENC delivery. Important patient-side facilitators of ENC include improving maternal knowledge of danger signs, so they know when to seek facility-based care (34, 35). Community-based educational initiatives, supplemented by education during antenatal visits, may improve maternal knowledge. Increased maternal education may promote facility-based births, which the Field Guide specifically encourages (7). A study in Darfur, for example, found that antenatal maternal health education was associated with a 43% reduction in home deliveries performed by TBAs (36). A community-based program that engaged with Rohingya mothers and community leaders in Bangladesh enabled an increase in facility-based birth and greater acceptance of delivery with skilled attendance and postnatal care with home visits (37). This study also provides an example in which some aspects of care were decentralized, through the employment of community midwives, in order to facilitate access.

Efforts to train and retain staff can improve ENC delivery in humanitarian settings. Trainings targeting high-impact ENC behaviors have the potential to decrease neonatal mortality through improvements in provider knowledge and attitudes (38). Trainings are beneficial when they are conducted in cross-functional teams, are complemented by mentorship, are linked to on-the-job observation and feedback mechanisms, and if refreshers occur regularly (15, 22, 23, 31). While the focus of this paper was ENC, it is important to note that trainings should also include interventions for small and ill babies, such as kangaroo mother care (KMC), timely antibiotic administration, and resuscitation (31, 39). Trainings may be complemented by shifting or sharing tasks when appropriate (26, 40). In addition to trainings, it is necessary to consider hiring locally and providing staff incentives, such as pay-for-performance and opportunities for advancement.

To be successful, trainings must also be accompanied by improvements at the facility and health system level. Infrastructure should be designed so mothers and babies can stay together for breastfeeding. Clinical protocols can help align care with high-quality standards while providing staff with just-in-time job support. Improvements in data collection at the facility level, including routine measurement of vital statistics, would not only allow for better measurement of service availability, coverage, and quality, but it would also allow for documenting needs and advocating for priorities (41). Facilities may also benefit from adopting neonatal signal functions related to essential and emergency care. These signal functions should be both aligned with service coverage targets from the Every Newborn Action Plan (ENAP), and adapted to humanitarian settings (3). They can be utilized in national, subnational, and facility-based assessments of service availability and coverage (42). Increasingly, these signal functions should be incorporated in assessments of quality of ENC, as outlined in guidelines WHO published in March 2022 (43). ENC is a central element of universal health coverage and must be incorporated into national and humanitarian packages of care.

The barriers and facilitators listed so far – related to patients, staff, and facilities – are shaped by the milieu in which they exist, namely the conflict settings themselves. While improvements in political stability and security would be conducive to the resumption of ENC services in humanitarian settings, "strategic" governance, or an approach in which the "minimal governance conditions required to implement" core ENC interventions may be sufficient, as has been demonstrated in several regions of instability and poor governance (6, 44). Other strategies, such as decentralization of operations and negotiated access to populations, also play a role in facilitating neonatal health interventions in humanitarian crises (40).

Limitations

This study is not without its limitations. African countries are heavily represented in this study, and there is a relative dearth of other regions. Despite this bias toward Africa, we may have missed the perspectives of regional Arabic- and French-language scholars due to our English language limitation. We limited our focus to interventions that primarily addressed the neonate. In reality, as the Roadmap to Accelerate Progress for Every Newborn in Humanitarian Settings 2020–2024 emphasizes, mother-baby dyads are central to understanding the continuum of ENC, which begins antenatally (45). Our focus on newborn interventions may not have allowed us to capture the full range of barriers and facilitators to ENC delivery by not adequately considering pregnancy and parturition. We also did not focus on prematurity, low birth weight, intrapartum complications, or serious bacterial infections, which are significant causes of morbidity and mortality in the neonatal period. ENC services must be linked with interventions targeting small and ill babies. Next, while a few quasi-experimental studies were included, most articles were cross-sectional or retrospective, reflecting the logistical and ethical obstacles related to conducting research in an insecure environment. This is reinforced by the fact that only academic, peer-reviewed literature was included in this review. Operational research, often reported through grey literature and conducted by aid organizations in the field, was omitted. Finally, most studies reviewed here utilized health facility data and did not review community-based strategies or home births. There is likely a selection bias, as data about mothers and babies who could not access facilities are missing from this review. Indeed, while the Field Guide encourages facility-based births whenever possible, community-based strategies for home births are important to consider when thinking about ENC holistically.

Conclusions

This systematic review outlines numerous barriers to ENC in humanitarian settings. Understanding barriers to ENC delivery will allow for the implementation of tailored strategies that can be aligned with international guidelines, such as ENAP, and adapted to humanitarian settings. Clarifying these barriers will not only strengthen service availability and coverage, but can also enable a renewed focus on improving the quality of newborn care in humanitarian settings.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The original contributions presented in the study are included in the article and /**Supplementary Material**. further inquiries can be directed to the corresponding author.

Author contributions

VK conceptualized and designed the study, collected and analyzed the data, drafted the initial manuscript, and critically reviewed and revised the manuscript. SM and AA contributed to data collection, carried out the initial abstract screening, and reviewed the manuscript. MC conceptualized and designed the study, contributed to data collection, and critically reviewed the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.937751/full#supplementary-material.

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EDITED BY
Ashish KC,
Uppsala University, Sweden

REVIEWED BY
Michael Wagner,
Medical University of Vienna, Austria
Jonathan Michael Davis,
Tufts University, United States

*CORRESPONDENCE
Linus Olson
linus.olson@ki.se

†These authors share last authorship

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Neonatal resuscitation monitoring: A low-cost video recording setup for quality improvement in the delivery room at the resuscitation table

Linus Olson[1,2,3,4]*, Xuan Anh Bui[5], Allan Mpamize[6], Hien Vu[7,8], Jolly Nankunda[9,10], Tung Thanh Truong[7], Josaphat Byamugisha[11], Tina Dempsey[4,12], Clare Lubulwa[9], Axel Winroth[13], Daniel Helldén[4], NeoSupra & NeoSpirit Teams, Anh Duy Nguyen[14], Tobias Alfvén[4,15], Nicolas Pejovic[4,15,16†] and Susanna Myrnerts Höök[4,15,16†]

[1]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden, [2]Training and Research Academic Collaboration (TRAC) Sweden - Vietnam, Hanoi, Vietnam, [3]Neonatal Department, Vietnam National Children's Hospital, Hanoi, Vietnam, [4]Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden, [5]Department of Information Technology, Phu San Hanoi Hospital, Hanoi, Vietnam, [6]Dr. Ronald Batte Hospital, Entebbe, Uganda, [7]Social Department, Phu San Hanoi, Hanoi Obstetrics and Gynecology Hospital, Hanoi, Vietnam, [8]Department of International Collaboration, Phu San Hanoi Hospital, Hanoi, Vietnam, [9]Mulago Specialized Women and Neonatal Hospital, Kampala, Uganda, [10]Department of Pediatrics and Child Health, College of Health Sciences, Makerere University, Kampal, Uganda, [11]Department of Obstetrics and Gynaecology, College of Health Sciences, Makerere University, Makerere, Uganda, [12]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Solna, Sweden, [13]Department of Medicine Huddinge, Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden, [14]Department of Hospital Administration, Phu San Hanoi Hospital, Hanoi, Vietnam, [15]Sachs' Children and Youth Hospital, Stockholm, Sweden, [16]Centre for International Health, University of Bergen, Bergen, Norway

Background: The quality of neonatal resuscitation after delivery needs to be improved to reach the Sustainable Development Goals 3.2 (reducing neonatal deaths to <12/1,000 live newborns) by the year 2030. Studies have emphasized the importance of correctly performing the basic steps of resuscitation including stimulation, heart rate assessment, ventilation, and thermal control. Recordings with video cameras have previously been shown to be one way to identify performance practices during neonatal resuscitation.
Methods: A description of a low-cost delivery room set up for video recording of neonatal resuscitation. The technical setup includes rechargeable high-definition cameras with two-way audio, NeoBeat heart rate monitors, and the NeoTapAS data collection tools for iPad with direct data export of data for statistical analysis. The setup was field tested at Mulago National Referral Hospital, Kampala, Uganda, and Phu San Hanoi Hospital, Hanoi, Vietnam.
Results: The setup provided highly detailed resuscitation video footage including data on procedures and team performance, heart rate monitoring, and clinical assessment of the neonate. The data were analyzed with the free-of-charge NeoTapAS for iPad, which allowed fast and accurate registration of all resuscitative events. All events were automatically registered and exported to R statistical software for further analysis.

Conclusions: Video analysis of neonatal resuscitation is an emerging quality assurance tool with the potential to improve neonatal resuscitation outcomes. Our methodology and technical setup are well adapted for low- and lower-middle-income countries settings where improving neonatal resuscitation outcomes is crucial. This delivery room video recording setup also included two-way audio communication that potentially could be implemented in day-to-day practice or used with remote teleconsultants.

KEYWORDS

video camera, NeoTap, NeoBeat, neonatal resuscitation, neonatal diagnostics, video recording, quality improvement

Introduction

The quality of neonatal resuscitation after delivery needs to be improved. In 2020 approximately 6,700 newborns died globally every day, 47% of all child deaths before 5 years of age. Most of these deaths occur during delivery, and the first day of life, and 98% in low- and middle-income countries (LMIC) (1, 2).

The Sustainable Development Goals (SDG 3.2) includes a specific target to end preventable neonatal deaths and decrease neonatal mortality to under 12 per 1,000 live births in all countries by 2030 (3). The most important causes of neonatal mortality are complications associated with preterm birth, birth asphyxia, or infections (4, 5). Birth asphyxia, and failure to initiate spontaneous breathing at birth, need early intervention, including warming, drying, and stimulation of the neonate. 3%–6% of all neonates need respiratory support with positive pressure ventilation (PPV) as part of the initial resuscitation (6). Delaying PPV leads to a progressive decrease in oxygenation and heart rate and potential death and/or brain injury in surviving neonates (7–10). Ventilation, early assessment of heart rate, and basic steps such as drying, and stimulation have been emphasized (11–16).

To improve neonatal resuscitation, we need to recognize what happens during this crucial time in a newborn's life, so we can review and optimize neonatal resuscitation to reduce unnecessary morbidity and mortality. This is true globally, from low- to high-resource settings. Furthermore, this is crucial in day-to-day services and clinical studies. It is essential to study neonatal asphyxia and its management in clinical settings. The need for basic and advanced resuscitation training and feedback for healthcare professionals, including doctors, midwives, and nurses, as well as teams, has been raised (17). A well-trained staff is key in all settings to reduce neonatal mortality (18).

We introduce a low-cost, still high-quality way of identifying performance practices during neonatal resuscitation using a video camera, heart rate meter (NeoBeat, Laerdal Global Health, Stavanger, Norway), and high-performance analyzing equipment (NeoTapAdvancedSupport, NeoTapAS, tap4life.org). The collected data can be used to improve resuscitation performance, including adherence to guidelines and closed-loop communication.

Our research team has used video cameras in previous studies and trials in Uganda, (19, 20) and others in the delivery room (21, 22). The NeoBeat dry-electrode ECG device is well adapted for LMIC where heart rate monitoring with a stethoscope is often not performed due to a lack of trained staff, stethoscopes, and pulse oximeters (23). The sensors pick up ECG-based signals recommended by The International Liaison Committee on Resuscitation (ILCOR) 2020 (7, 10) as the most reliable way to measure newborn heart rate (24). NeoTapAS for iPad was developed by members of our research group to register events during neonatal resuscitations and has been evaluated by our team and others (17, 25–28).

In this methodology article, we introduce a comprehensive technical framework for monitoring newborn resuscitation and explain how it was implemented in two different settings: Kampala, Uganda, a low-income setting, and Hanoi, Vietnam, a lower middle-income setting.

Materials and equipment

This low-cost video recording setup for quality improvement in the delivery room includes:

a) Video cameras and video storage:

- Cameras: HD 1080P Black Box AI-IP018 (Shenzhen Aishine Electronics) (Uganda).

  HD 1080P PIR Black Box Wi-Fi Security Camera AI-IP018 cameras (Shenzhen Aishine Electronics) (Vietnam).

  (HD-DV018 1080P Black box PIR Security Camera, AI (Shenzhen Aishine Electronics) (First used in Vietnam but later taken away).
- Memory space: SD card (SanDisk, Western Digitals, Milpitas, CA, USA) 128 GB with space for up to 3.5 days of recording.

- Hard drives, one for raw footage storage and one for cut version, 4 TB (Western Digital My Passport, Milpitas, CA, USA).
- Homemade heat-proofed camera cases.
- Software for cutting and mending data: Adobe Premiere Pro 64-bit version (Adobe Systems Inc., Adobe, San Jose, CA, USA).

b) Heart rate monitoring equipment: NeoBeat Newborn HR Meter (Laerdal, Stavanger, Norway).
c) iPad platform with software NeoTapAS for video analysis.
d) Statistical software R.
e) Local resuscitation table.
f) Hospital-based neonatal resuscitation guidelines.

In the list above, we used specific brands for practical quality reasons. However, similar equipment can be used.

Methods

We describe a low-cost monitoring setup for the resuscitation table in the delivery room. This method helps to identify the process and actions of staff procedures to improve the quality of care. The method has been used at Mulago National Referral Hospital, Uganda, and Phu San Hanoi Hospital, Vietnam.

Methodology setup

First step

We reviewed existing procedures and equipment, the organization of the resuscitation team, and current guidelines. This included discussions with the administration and clinical staff of the hospitals about how to minimize interference of monitoring with current practices and information about the study and equipment aimed to be used.

Second step

At both sites, ethical approval was sought from the local institutional review boards. The decision regarding the number of cameras and NeoBeat monitors needed for the studies was done according to where most neonatal resuscitations took place at the hospitals.

Third step

The equipment was installed to identify potential technical problems before the training of the staff. Cameras were placed at each resuscitation table away from the high-temperature area of the heater to capture exact footage of the newborn and the hands of the providers, eliminating the risk of staff identification. Also, placement was optimized for easy SD card access needed for the data collection. Tables were adapted to fit the cameras within the recommended focus range, between 60 and 120 cm. Cables and NeoBeat chargers (24) were also placed on the resuscitation table to facilitate access and minimize interference in normal clinical practice.

Fourth step

Midwives, doctors, nurses, and technical staff were introduced to the study setup and trained in equipment management. Hospital executives were informed about practice changes, and cleaning staff were trained to avoid tampering with the new setup.

Fifth step: clinical usage

Uganda

Video cameras HD 1080P Black Box AI-IP018 (Shenzhen Aishine Electronics) were installed at three out of four resuscitation tables at Mulago National Referral Hospital, Kampala, Uganda, and recorded data around the clock. The cameras were placed so that only the hands of the resuscitator and the neonates were recorded. The SD cards of each camera were swapped every day to ensure that all recordings were properly saved (**Figure 1A**). In case technical issues were noticed, the study coordinator or trial investigator was notified for corrective measures. NeoBeat heart rate meters were installed for a sub-study, and therefore only used for part of the newborns. It was placed directly around the neonates' abdomen, providing a fast and accurate continuous display of heart rate visible on the videos during the review process (29). Inclusion criteria were neonates born in the hospital, estimated gestational age of at least 34 weeks, estimated birth weight of at least 2,000 g, and need of PPV at birth. Exclusion criteria were major malformations (incompatible with sustained life or affecting the airways) and stillbirths. All neonates fulfilling the eligibility criteria for each clinical study (please find the separate clinical criteria in references by Myrnerts Höök et al., Pejovic et al., and Larsson et al.) were filmed and enrolled (30, 31).

Each morning and afternoon, the camera data manager checked the cameras to ensure that they functioned well, including power control and the orientation of the camera. In case of problems, the study coordinator or trial investigator was notified for corrective measures. Power banks were used to keep the cameras running in case of a power shortage. The steps of retrieving and saving data are summarized in step six. After retrieving data, each resuscitation of the day was identified by the data managers and shown to one of the study doctors to ensure that it was a case of need of PPV and that the complete case was caught on video.

Vietnam

Video cameras HD 1080P PIR Black Box Wi-Fi Security Camera AI-IP018 cameras (Shenzhen Aishine Electronics) (32) were installed above 7 out of 12 Phu San Hospital resuscitation tables, Hanoi, Vietnam, and recorded data around the clock.

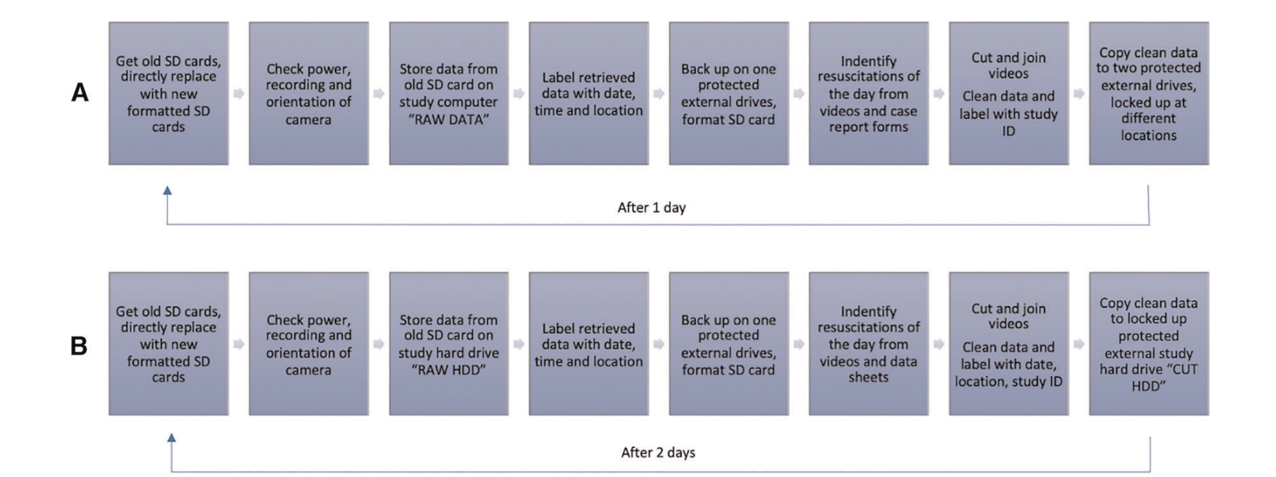

FIGURE 1
Video camera process for Uganda (A) and Vietnam (B) from the insertion of SD card into camera to video recording and final cut ready for analysis.

The cameras were placed so that only the hands of the resuscitator and the neonates were recorded (**Figure 2**). Inclusion criteria were born in a hospital, and need for PPV at birth. There were no exclusion criteria. The SD cards of each camera were swapped every second day (but the cards used could handle data up to 3.5 days) to ensure that all recordings were properly saved (**Figures 1B**). In case technical issues were noticed, the study coordinator or trial investigator was notified for corrective measures (**Figure 3**). NeoBeat heart rate meters were installed at each of the seven resuscitation tables (33), and used in the same way as above for the newborns with placement around the neonates' abdomen, providing a fast and accurate continuous display of heart rate visible on the videos during the review process (33).

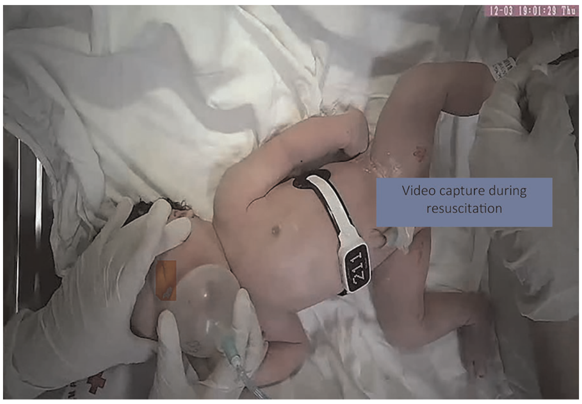

FIGURE 2
A real capture from a video showing the situation at the resuscitation table with NeoBeat on the neonate's chest and only hands shown.

Sixth step: collection of data

Each camera's footage was secured by swapping the SD card and checking that the camera was recording the correct angle. The SD card with the latest data was downloaded onto the first hard drive (4 TB, Western Digital My Passport Milpitas, CA, USA) and marked RAW, identifying the date, and camera. The data were stored in folders with formats as follows:

- RAW: Date -> Camera number -> Videos

The technical staff downloaded all video data including identified resuscitations. The time when the resuscitations took place was recorded by the attending midwife or doctor. The sections with important data were selected using Adobe Premiere 64-bit version and transferred to storage in a 4 TB hard drive. A final evaluation of the resuscitation recordings was performed by a study doctor, also checking for missing data. The videos were stored in folders with formats as follows:

- CUT: filename of videos (ORDERNO_DDMMYY_ LOCATION_ CAMNUM_PATIENTID) Patient ID was a generated study number.

Seventh step: data management for analysis

Data extracted from the video recordings as well as maternal and neonatal characteristics were collected using standardized hard-copy case report forms. Resuscitation data were collected by analysis of the videos, using the NeoTapAS (34) app for real-time data registration during neonatal procedures (25, 26). Recorded data were directly exported for statistical analysis.

Statistical methods

We used the free R statistical software [see previous papers (19, 33)]. The code documentation and scripts are available on

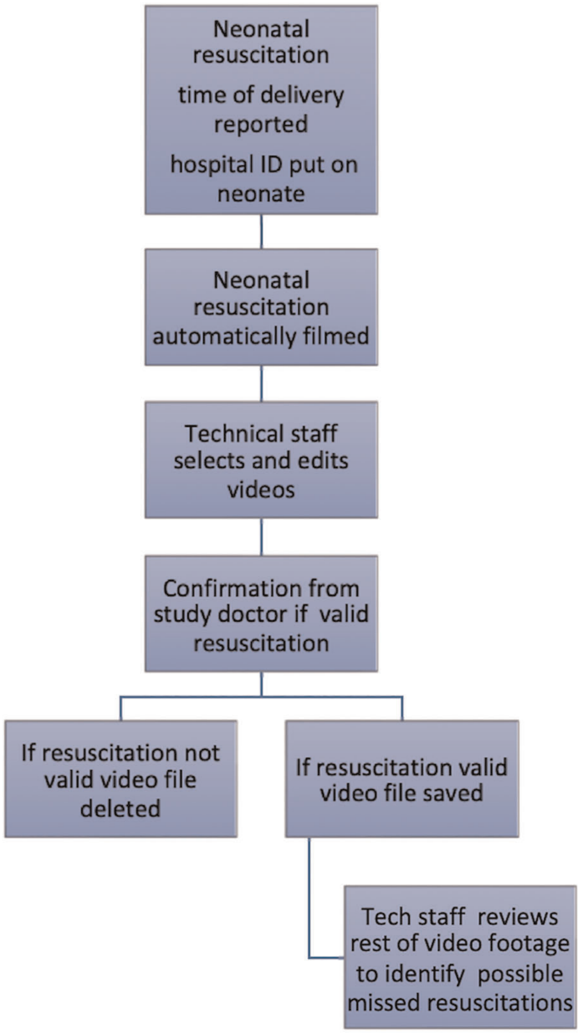

FIGURE 3
The process from delivery to verified video captured resuscitation, Uganda, and Vietnam.

request. Example scripts used to reproduce the figures have been published on GitHub were also the R package with functions and example data can be found. https://github.com/Global-child-health-SDGs-Team-KI/Neonatal-Resuscitation.

Data management

At both study sites, all study-related information obtained was handled confidentially. All participant information, including case report forms, lists, logbooks, and any other listings linking participant ID numbers, was stored in locked file cabinets in areas with limited access. Research teams could only identify participants using a locally stored key file linked to the study numbers. Raw files were stored on a primary drive, cutout videos on a secondary drive, and backup copies were stored in a remote location (**Figure 1**). Videos were stored in a locked safe and hard drives were password protected. To help with the usage of the method, the collection types, variables used, and codes are available on request even if the real collected data due to ethical considerations cannot be shared.

Ethical considerations

The protocol for the Ugandan study was approved by the Institutional Review Board of Mulago National Referral Hospital, Uganda (MHREC 1168), the Uganda National Council of Science and Technology; the Director-General from the Ministry of Health, Uganda (MREC 1168); and the Regional Committee for Medical and Health Research Ethics (REK South-East reference number 2017/989) in Norway. The protocol for the Vietnamese study was approved by the Institutional Review Board at Dinh Tien Hoang Institute of Medicine, the Ethical Review Board of Hanoi (No: IRB-2001 and IRB-2002), and the Swedish Ethical Review Authority (Dnr 2021-00064/2021-03-01).

Video recording with ethical considerations is today the standard for data collection in neonatal resuscitation (21, 35–37). Only the neonate and the hands of the resuscitator were visible, and the video audio was muted. The identity of neonates and resuscitators were kept anonymous. Video recordings were not used for malpractice cases. Thus, no consent was required from the resuscitators. All staff involved at both sites in neonatal resuscitations got at least one information session prior to study commencement. If the parents of the neonate did not consent to participate in the study, the video recordings were deleted and safely discarded.

Results

The technical setup focused on neonatal resuscitation in two LMICs and had parallel protocols. We anticipated that the setups could produce data about the procedures and team performance in both LMICs. Below we summarize our experiences in the two different study settings.

Uganda

Cameras were susceptible to overheating, and two cameras had to be replaced because of battery swelling. This happened although the resuscitation table heaters at Mulago Hospital were not in use. Power shortage was challenging but solved by connecting extra power banks to the cameras. We had cameras offline to avoid unsafe transferring data *via* Wi-Fi. The high quality of the camera footage allowed us to zoom in during the review, using standard software to identify additional details. A hanging kit using steel wires and duct tapes was made to secure the cameras. However, these hanging kits were difficult to reuse and magnetic adjustable camera mounts improved operations.

A total of 17,505 eligible neonates were born in the hospital during the study period of which 16,781 provided oral consent and 1,439 needed PPV. None were excluded because of missing video or poor quality. In total, 268 neonates were excluded due to other reasons. Thanks to the video reviews eight neonates were withdrawn from the main trial (four were fresh stillbirths, two did not need PPV, and two had major dysmorphic features) (31).

For handling case report form data collected simultaneously as video data, we used a Fujitsu iX1500 scanner to help us export the data for inclusion in our electronic database (38).

Vietnam

To avoid overheating the cameras, we used three different setups. Staff surrounding the tables were trained to address possible overheating and avoid moving the camera angle (**Figures 4A,B**). In the most intensive resuscitation tables, we found two cameras that overheated, and the shell melted, causing another view angle than intended. The original chargers were prone to failure (the USB port and camera cable breaking or losing contact), but third-party chargers solved the problem.

We initially used an HD-DV018 1080P Black box PIR Security Camera, AI (Shenzhen Aishine Electronics) (32). However, cameras with internal network HD 1080P Black Box AI-IP018 cameras (Shenzhen Aishine Electronics) and an app for IOS or Android (supposed to be fully functional but not fully tested by our team) for remote check improved trimming of camera angles. High-definition video data allowed us to identify additional details. The compatibility of the camera management application was limited as it only supported IOS for iPhones. The cameras did not have a hanging kit, so the installation of the cameras was made in a similar way as explained above for Uganda. The Software of the cameras was changed between models from pro version 1 to pro version 2. The new version improved stability during power cuts and program performance. However, problems with inaccurate time stamps on videos and shut-down operation of two-way audio recording still need to be addressed with software updates (**Figure 5**).

Midwives were unfamiliar with the new NeoBeat heart rate monitors (24) and needed training. The research teams' subjective view is that NeoBeats were found to be user-friendly, and both midwives and doctors found them helpful for clinical assessments. During the study, we also used NeoBeat for neonates that were smaller than recommendations, often with a continuously displayed heart rate despite a birth weight <1,500 g and using a plastic bag. We did not compare the displayed heart rate with heart auscultation but have no reason to mistrust its accuracy. NeoBeat has now become essential equipment during newborn resuscitation at the Phu San hospital.

A total of 18,107 eligible neonates were born in the hospital during the study period of which 75 needed PPV. Fifty-seven neonates who received PPV were captured on a

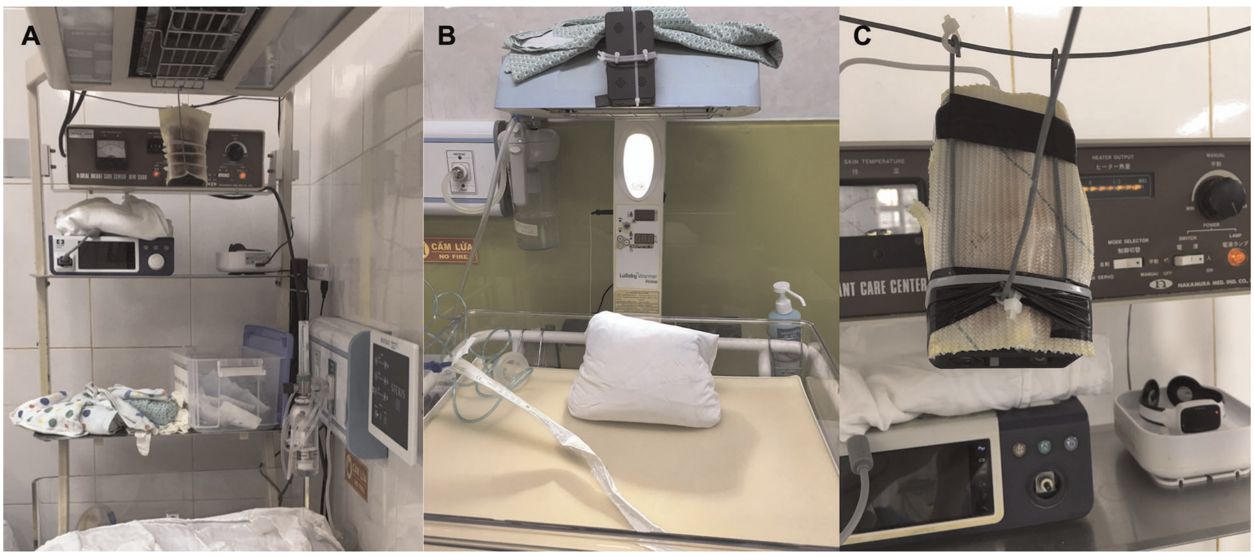

FIGURE 4
(A) The capture of setting up version 1. (B) The capture of setting up version 2. (C) Camera close-up.

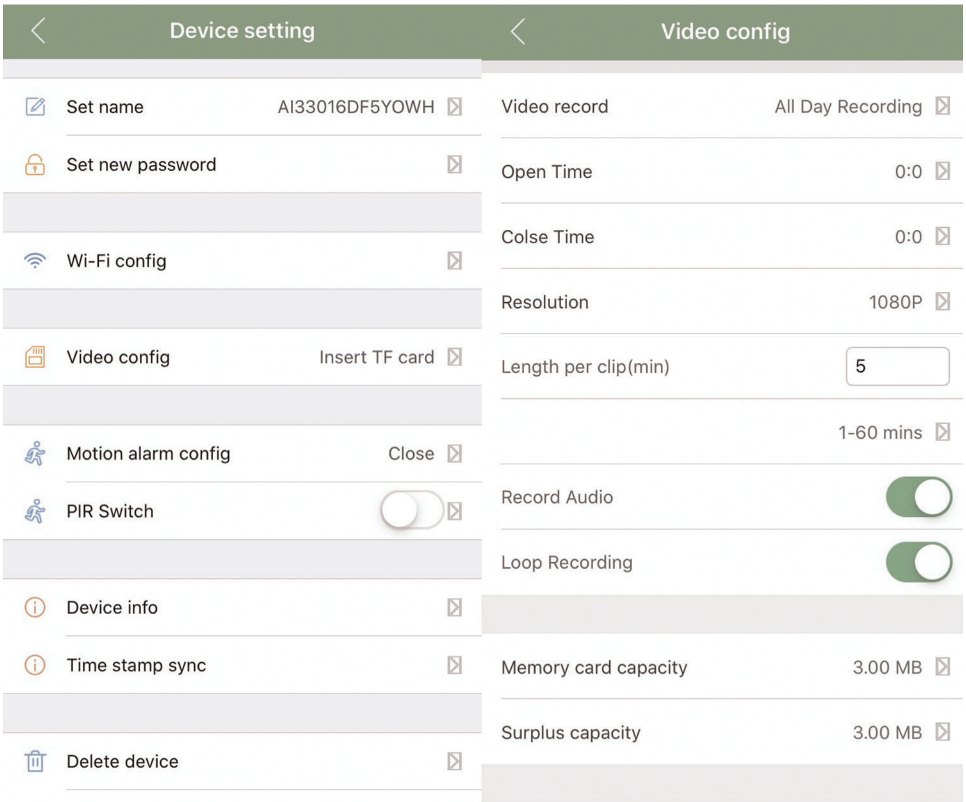

FIGURE 5
App software of the camera in Vietnam.

video camera, of which all provided oral consent. Thirty-six neonates required endotracheal intubation of which 24 were captured on video camera. The reasons for the neonates that were not captured on video recordings were: resuscitation on location with no camera (main reason); a problem with the camera (broken, not charged). No videos had poor quality. No neonates were withdrawn from the study after the video review.

For handling case report form data collected simultaneously as video data, we used a Fujitsu iX1500 scanner to help us export the data for inclusion in our electronic database (38).

Documentation of neonatal resuscitation practices

The quality of the overall documentation of neonatal resuscitation in medical charts has been investigated and points to an urge to improve documentation to evaluate resuscitation practices (39). In Uganda, midwives were informed to record with a stopwatch, the time from the start of ventilation to the end when the resuscitation device was removed from the baby's mouth. Times were noted in the case report forms. When reviewing the videos, we saw that the ventilation times were inaccurate and could not use the data in the first published paper (31). In a recent sub-study (29), ventilation time was recorded by looking at the videos and recording the time of start and stop of ventilation. A comparison of ventilation time from the case report forms and this method is noted in **Table 1**. This points to the benefit of not just relying on on-site documentation by individuals for reliable data.

In summary, we collected detailed resuscitation video footage with data showing the procedures done by the staff hands at the resuscitation table, including stimulation, ventilation, intubation, and heart rate monitoring with NeoBeat. NeoTapAS allowed fast and accurate registration of all events during video review. All events were automatically summarized in Excel format in a report ready for export. The information could then be directly exported to other statistical programs, such as R, for further analysis. The video footage provided crucial information to improve the quality of care during neonatal resuscitation in the delivery room.

Important lessons learned:

– Staff should be informed to notify data managers early if problems occur.

TABLE 1 Case report form vs. video review.

No	Ventilation time* noted in case report form in seconds	Ventilation time* according to video review in seconds
1	1,345	2,100
2	57	60
3	112	189
4	44	52
5	40	55
6	895	2,171
7	95	120
8	1,250	1,412
9	131	169
10	90	92
11	650	1,007
12	387	2,560
13	330	490
14	76	87
15	112	110
16	121	100
17	65	85
18	80	68
19	57	102
20	245	284
21	80	117
22	54	87
23	128	125
24	108	118
25	131	136
26	150	263
27	308	376
28	324	402
29	690	726
30	113	197
31	18	19
32	369	2,254
33	1,086	1,370
34	250	287
35	800	888
36	83	121
37	396	2,266
38	291	592
39	109	168
40	118	195
41	194	261
42	105	162
43	101	192
44	48	54
45	798	983
46	46	57
47	707	886
48	39	56

*Ventilation time is the time in seconds from the start of ventilation to the end when the resuscitation device is removed from the baby's mouth.

- Each resuscitation table should have a charging station or extra batteries.
- High-definition cameras with a minimum storage of 3.5 days are essential to eliminate the risk of running out of data storage if for unexpected reasons not changed according to plan.
- In both settings, it got very hot at the resuscitation tables and the cameras were sensitive to heat, so we needed to protect the video cameras. In both LMIC settings, we have done this by optimizing/changing the placement of the camera and putting different kinds of heat shields around the most sensitive parts of the cameras and internal battery, as shown in **Figures 4A–C**.
- NeoBeat charging routines and correct placement of the device on the baby's abdomen are critical for accurate data collection.
- Even if relatively low-cost and easy to install, selecting the resuscitation tables where the equipment should be installed is important. Each extra camera takes time and adds an extra burden.
- Video analysis for data documentation during neonatal resuscitation is not a perfect alternative. It is sometimes difficult to assess the quality of ventilation and the depth of suctioning. It is never possible to see the endotracheal tube position. The heart rate and saturation monitor needs to be placed so that they can be viewed on the video recordings, and even if the NeoBeat heart rate monitor is used it can sometimes be difficult to see the digits due to light reflections.

If ethical approval allows, the video recordings can be used for training purposes and staff debriefing.

Discussion

We describe a method for a low-cost video recording setup for quality improvement at the newborn resuscitation table. The technical framework, data collection, and analyses used in one low- and one LMIC for identifying resuscitation procedures can provide highly detailed resuscitation video footage including data on procedures and team performance, heart rate monitoring, and clinical assessment of the neonate.

Video recording for data documentation during neonatal resuscitation is increasingly regarded as a golden standard of practice. Both our own (19, 20, 29, 30) and other (6, 21, 22, 27, 35, 40) research teams have previously conducted similar studies. Usage of video recording, heart rate monitoring, and NeoTapAS in these studies were useful tools to identify performance at the resuscitation table (17, 19, 20, 28–31, 33, 41) and improve data collection. This method may be helpful for a better understanding of patients included in studies and treatment of hypoxic-ischemic encephalopathy (HIE) after resuscitation (41).

Video footage also provided objective feedback on staff practice and performance, helping them to improve practice regardless of the research outcome. Progress in clinical practice during data collection is a confounder from a research perspective but justified in the context of site-specific quality improvement programs. The technical setup also holds the potential to be used in telemedicine programs in the future.

We encountered technical issues such as overheating of cameras and software problems, but these issues were swiftly addressed. In recent studies, we used cameras with improved heat control, updated software (42), and higher resolution. These updates created a solid data collection setup and serve as an additive to the traditional setup used in Uganda and Vietnam to identify neonates in need of PPV. Video evaluation allows screening and documentation of cases of neonatal birth asphyxia in risk of HIE and staff debriefing. This setup could also contribute to aligning current hospital guidelines with best practice recommendations including improving the quality of neonatal resuscitations.

This low-cost video recording setup has been used to monitor neonatal resuscitation. However, this method has the potential to be applied within a range of different areas to improve upon skills, procedures, and learning from experience, e.g., emergency care and trauma care.

Video recordings can support staff debriefing and be embedded in site-specific quality improvement programs. The recordings can be used when training close-loop communication, in debriefings after complicated resuscitations with unpredicted results, and in general quality improvement programs focusing on neonatal resuscitation team training.

Conclusions

Video analysis of neonatal resuscitation is an emerging quality assurance tool with the potential to improve neonatal resuscitation outcomes. The setup is well adapted for low- and lower-middle-income settings where improvement of neonatal resuscitation outcomes is crucial. The cameras also support two-way audio communication and could potentially be used with remote tele leaders or teleconsultants in the future.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://github.com/Global-child-health-SDGs-Team-KI/Neonatal-Resuscitation.

Ethics statement

The studies involving human participants were reviewed and approved. The protocols for the Ugandan study was approved by the Institutional Review Board of Mulago National Referral Hospital, Uganda; the Uganda National Council of Science and Technology; the Director-General from the Ministry of Health, Uganda (MREC 1168); and the Regional Committee for Medical and Health Research Ethics (REK South-East reference number 2017/989) in Norway. The protocol for the Vietnamese study was approved by the Institutional Review Board at Dinh Tien Hoang Institute of Medicine, the Ethical Review Board of Hanoi (No: IRB-2001 and IRB-2002), and the Swedish Ethical Review Authority (Dnr 2021-00064/2021-03-01). In the image showing a patient in the manuscript, the patients' guardians have given full written consent. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors have made substantial contributions to either design, set-up, acquisition and interpretation of data. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

SMH, NP, CL, and TA are co-founders of the non-profit organization Tap4Life (www.tap4life.org), which produced the free-of-charge application NeoTapAS. The authors do not receive any salary from Tap4Life.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Andrew Steenhoff,
Children's Hospital of Philadelphia, United States

REVIEWED BY
Michael Espiritu,
Weill Cornell Medical Center, NewYork-Presbyterian, United States
Waldemar Carlo,
University of Alabama at Birmingham, United States

*CORRESPONDENCE
M. Patel
mariam.patel111@gmail.com

[†]These authors share senior authorship

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Hypothermia in neonates born by caesarean section at a tertiary hospital in South Africa

Mariambibi Patel[1*], Neo Ramagaga[1], Danielle Kruger[1], Grace Lehnerdt[1], Imraan Mansoor[1], Lesedi Mohlala[1], Dylan Rendel[1], Fathima Zaheed[1], Mimie Jordaan[2], Mantoa Mokhachane[1], Firdose Lambey Nakwa[1,3†] and Ramatsimele Mphahlele[2†]

[1]University of the Witwatersrand, Faculty of Health Sciences, Johannesburg, South Africa, [2]District Clinical Specialist Team, Johannesburg Health District, Johannesburg, South Africa, [3]Department of Paediatrics and Child Health, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

Introduction: neonatal hypothermia has previously been noted in a large proportion of neonates born through Caesarean section at Chris Hani Baragwanath Hospital (CHBAH), yet no study in South Africa specifically explores the extent and severity of the threat of hypothermia to this population of neonates.
Objectives: to describe the proportion and severity of neonatal hypothermia in infants born *via* Caesarean section at CHBAH as well as to document and describe possible contributing factors to neonatal hypothermia in this population.
Methods: A neonatal unit's database records were reviewed for demographic information of patients and their mothers, clinical characteristics, body temperature and outcomes. Comparisons between normothermic and hypothermic neonates were performed.
Results: Forty-one percent of neonates born *via* Caesarean section had hypothermia at birth, of whom 71%, 27% and 2% had mild, moderate and severe hypothermia, respectively. Prevalence of admission hypothermia was 42%. On average, neonates were born at term and were of normal birth weight. No maternal factors were found to be statistically significant. Bag-mask ventilation (BMV) and cardiopulmonary resuscitation (CPR) [3.4% vs. 0.7%, *p*-0.033; OR 2.67 (95% CI: 1.06–6.77)] and an elevated lactate [13.25 vs. 3.2 mmol/l, *p*-0.032; OR 1.13 (95% CI: 1.01–1.26)] were associated with hypothermia. In the multivariable logistic regression analysis hypothermia in neonates was associated with an elevated lactate.
Conclusions: Prevalence of hypothermia in neonates born by Caesarean section is high and further prospective studies are required to elucidate the factors contributing to this.

KEYWORDS

hypothermia, neonate, caesarean section, season, birth weight

Introduction

The third sustainable development goal proposed by the World Health Organization speaks directly to improving healthcare. Surrogate measures for the healthcare of a country are the maternal and childhood mortality rates. Neonatal mortality in South Africa can be attributed to five main causes: prematurity, intrapartum events, infections, congenital abnormalities and miscellaneous causes (1). Hypothermia in neonates is known to contribute to neonatal mortality due to neonatal infections, prematurity and asphyxia (2).

Neonatal hypothermia was noted in a large proportion of neonates born through Caesarean section in data collected during a baseline audit for a Quality Improvement by the EMS services, yet no study in South Africa specifically explores the extent and severity of the threat of hypothermia to this population of neonates. A retrospective review at Chris Hani Baragwanath Academic Hospital (CHBAH) showed that hypothermia in neonates had a significant association with neonates born at 1 000 g (OR = 1.79), those requiring resuscitation (OR = 2.32) and, in contrast to other studies, were more likely to be born vaginally (OR = 1.48). This was proposed to be due to poor temperature control in delivery rooms as opposed to operating theatres and due to the fact that neonates born of Caesarean section were more likely to be attended to by a doctor, resulting in better control of temperature. The study also reports a higher mortality rate in hypothermic infants within a week of delivery (3). The severity of hypothermia in this study was not specified. This study thus aims to describe the proportion and severity of neonatal hypothermia in infants born *via* Caesarean section at CHBAH. The study also aims to document and describe possible contributing factors to neonatal hypothermia in the study population.

Methodology

A retrospective descriptive study was undertaken at Chris Hani Baragwanath Academic Hospital (CHBAH) Neonatology Unit for the period 1 January 2018 to 31 December 2018. The CHBAH neonatology unit comprises of an 18 bed neonatal intensive care unit (NICU), a 48 bed high care area, a 100 bed standard care nursery (SCN), a 19 bed Kangaroo Mother Care (KMC) ward. Approval for the retrospective review of the CHBAH Neonatology Unit's database was granted by the Human Research Ethics Committee [HREC] (Medical) in July 2020. Ethics amendment was applied for and granted in March 2021.

The study population included all neonates born *via* Caesarean section at CHBAH and excluded patients born outside of CHBAH – for example transferred into the hospital or born before arrival (BBA) and those patients without any body temperature data available.

The data collected was secondary in nature, as it was collected from the Research Electronic Data Capture (REDCap) database of the CHBAH Neonatology Unit. The variables collected included: season of birth, birth weight, gestational age, body temperature, 1-minute APGAR score, neonatal biochemical parameters, indication for Caesarean section, resuscitation outcomes, neonatal illnesses as well as a number of maternal factors (age, parity, gravidity, race, HIV status, antenatal care received, antibiotics received, antenatal steroids administered and complications). Hypothermia was defined as an axillary temperature below 36.5 °C as per the World Health Organization (WHO) (4). This was further stratified into mild (36 °C–36.4 °C), moderate (32 °C–35.9 °C) and severe hypothermia (<32 °C). An axillary temperature within 30 min of birth was regarded as the birth temperature. The 4 seasons were defined as spring from 1 September to 30 November, summer from 1 December to 28 February, autumn from 1 March to 31 May and winter from 1 June to 31 August. A normal birthweight (NBW) was defined as a weight between 2.5 and 4.0 kilograms (kg), macrosomia as > 4.0 kg, low birthweight (LBW) as < 2.5 kg, very low birthweight (VLBW) < 1.5 kg and extremely low birthweight (ELBW) as < 1 kg.

Anonymised data was analyzed with aid of the statistical package Stata (version 16). Chi-square tests were used to determine statistical significance of categorical variables. Continuous variables were analyzed as normally or non-normally distributed using histogram functions. Statistical significance of continuous variables was determined by *t*-tests and Mann-Whitney *U* tests (Wilcoxon Rank Sum test) for normally and non-normally distributed variables respectively. Logistic regression models were used to determine odds ratios. For the multivariable regression model variables with a *p*-values <0.1 were included and those variables with few observations were excluded. The meconium aspiration variable was omitted from the linear regression due to no observations in the non-hypothermia group.

Results

Of the 1,049 neonates born by Caesarean section at CHBAH during the study period, 1,017 (96.95%) were enrolled into the study (**Figure 1**). Forty-one percent ($n = 421$) had hypothermia at birth, of whom 71% ($n = 299$), 27% ($n = 114$) and 2% ($n = 8$) had mild, moderate and severe hypothermia, respectively (**Figure 1**). Additionally, of the 299 infants admitted to the neonatal wards at CHBAH, 42% ($n = 125$) were hypothermic (**Figure 2**). There were no significant differences when divided into mild, moderate and severe hypothermic groups.

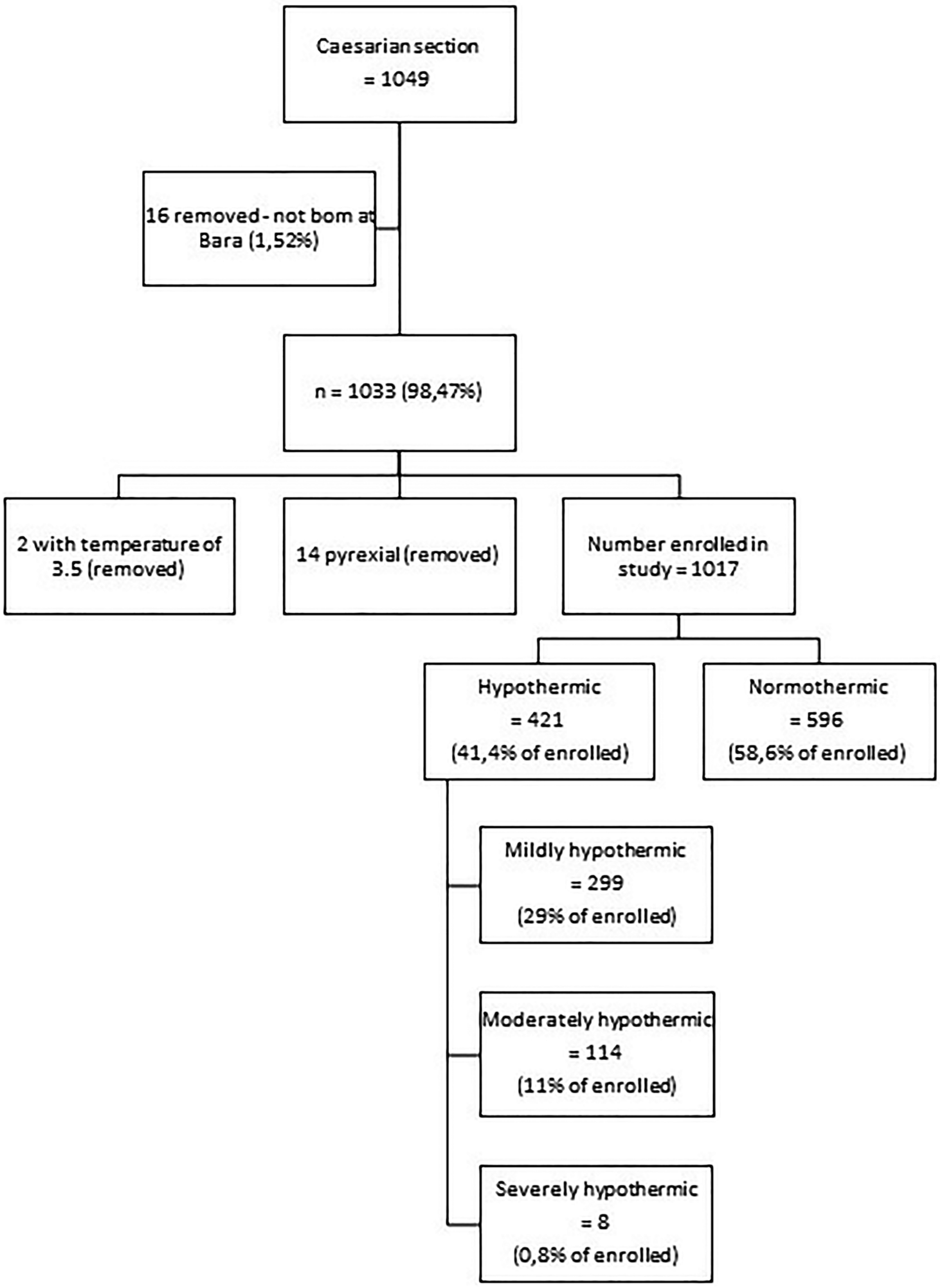

FIGURE 1
Consort diagram.

(Figure 2). The admitted infants were a subset of the study participants.

Maternal characteristics

Most mothers in our study were African, with no Caucasians. They had a mean age of 28.4±6.6 years and were having their second child (mean 2±2). 25.3% were HIV positive and only 4.6% did not receive antenatal care. Receiving antibiotics, steroids or magnesium sulphate was not found to be associated with neonatal hypothermia (Table 1). The commonest indication for Caesarean section was foetal distress (64.7%). Neonates requiring Caesarean section for intrauterine growth restriction (IUGR) were less likely to be hypothermic [0% vs. 2.1%, OR 0.09 (95% CI: 0.00–0.56)] (Table 2).

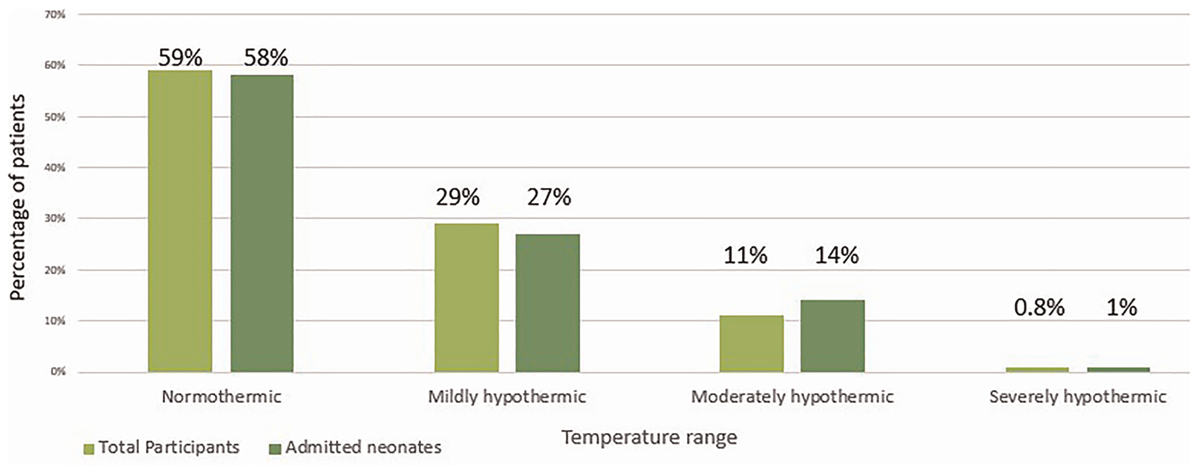

FIGURE 2
Comparison of severity of hypothermia amongst total and admitted neonates.

TABLE 1 Maternal characteristics of study population.

Maternal factors	All *n*/*N* (%)	Hypothermic *n*/*N* (%)	Normothermic *n*/*N* (%)	*p*-value	Odds-ratio (95% CI)
Age*	28.4 ± 6.6	28.4 ± 6.6	28.5 ± 6.6	0.852	0.998 (0.98–1.02)
Parity#	1 (0–2)	1 (0–2)	1 (1–2)	0.238	0.94 (0.85–1.04)
Gravidity#	2 (1–3)	2 (1–3)	2 (1–3)	0.870	1.01 (0.91–1.11)
Unbooked	48/989 (4.6)	18/407 (4.4)	30/582 (5.2)	0.598	0.60 (0.33–1.08)
African Race	980/999 (98.1)	407/414 (98.3)	573/585 (98.0)	0.906	0.93 (0.62–1.39)
Maternal antibiotics	81/876 (9.2)	37/368 (10.1)	44/508 (8.7)	0.482	1.18 (0.74–1.87)
Maternal steroids	128/912 (14.0)	57/382 (14.9)	71/530 (13.4)	0.513	1.13 (0.78–1.65)
Maternal MgSO4	69/884 (7.8)	32/369 (8.7)	37/515 (7.2)	0.416	1.22 (0.75–2.00)

*Mean ± SD.
#Median, IQR.
Missing values: Rh (*n* = 20), RVD (*n* = 25), RPR (*n* = 51), booked (*n* = 28), maternal antibiotics (*n* = 141), maternal steroids (*n* = 105), maternal MgSO4 (*n* = 133), parity (*n* = 5), gravidity (*n* = 7), age (*n* = 9).

Neonatal characteristics

Twenty-five percent of the study population (*n* = 251) were HIV exposed, 14% (*n* = 128) received antenatal steroids, 54% (*n* = 508) were male, 33% (*n* = 323) were premature and 21.9% (*n* = 169) were exposed to meconium. The mean gestational age and birth weight were 37.1 (±3.54) weeks, 2766.4 (±796.1) grams respectively. In 19.4% (*n* = 196) of neonates, the 1 min Apgar score was <7. Neonates who were exposed to meconium were less likely to be hypothermic [18.2% vs. 24.6%, OR 0.68 (95% CI: 0.48–0.99)] (Table 3). Hypothermic neonates were mostly born in spring followed by winter (Figure 3) and most were of normal birth weight (Figure 4). In addition, there were a larger number of deliveries in spring (5030) followed by winter (4799). Approximately 18.7% (*n* = 171) of all the neonates required resuscitation at birth (Table 4). Neonates who received both bag mask ventilation (BMV) and cardiopulmonary resuscitation (CPR) were more likely to be hypothermic than those who did not [3.4% vs. 0.7%, OR 2.67 (95% CI: 1.06–6.77)] (Table 4). However, other respiratory interventions such as nasal cannula, nasal continuous positive airway pressure (nCPAP), receiving surfactant or assisted ventilation were not significantly associated with the temperature of neonates. Being hypothermic increased the likelihood of having an elevated lactate [median lactate of 13.25 vs. 3.2 mmol/l, OR 1.13 (95% CI: 1.01–1.26)] (Table 5). Only a small proportion of neonates had an arterial blood gas (ABG) drawn as ABGs are only done in sick neonates.

Morbidity and mortality outcomes

Overall, 39.7% (*n* = 404) of the neonates were found to have a respiratory pathology, 2.5% (*n* = 25) were asphyxiated, 0.8%

TABLE 2 Indication for caesarean section.

Caesar Indication	All $N = 881$ n (%)	Hypothermic $N = 362$ n (%)	Normothermic $N = 519$ n (%)	p-value	ORs (95% CI)
Abnormal foetal presentation	25 (2.8)	962 (2.5)	16 (3.1)	0.600	0.80 (0.35–1.84)
Hypertensive disorders of pregnancy	84 (9.5)	40 (11.0)	44 (8.5)	0.201	1.34 (0.85–2.12)
Placental abnormalities	15 (1.7)	7 (1.9)	8 (1.5)	0.658	1.25 (0.45–3.50)
Abnormal labour	44 (5.0)	15 (4.1)	29 (5.6)	0.333	0.73 (0.39–1.38)
Foetal distress	570 (64.7)	242 (66.9)	328 (63.2)	0.264	1.17 (0.89–1.56)
CPD	35 (4.0)	17 (4.7)	18 (3.5)	0.359	1.37 (0.70–2.7)
Multiple pregnancies	41 (4.7)	11 (3.0)	30 (5.8)	0.057	0.51 (0.25–1.03)
Premature	7 (0.8)	3 (0.8)	4 (0.8)	0.924	1.08 (0.24–4.84)
Previous Caesar	125 (14.2)	47 (13.0)	78 (15.0)	0.392	0.84 (0.57–1.25)
IUGR	11 (1.2)	0 (0.0)	11 (2.1)	0.005	0.09 (0.0–0.56)
APH	32 (3.6)	14 (3.9)	18 (3.5)	0.755	1.12 (0.55–2.28)
Macrosomia	8 (0.9)	1 (0.3)	7 (1.3)	0.099	0.20 (0.02–1.65)

Missing:- $n = 136$.
Abnormal foetal presentation refers to breech, oblique lie, cord prolapse and face presentation.
Hypertensive disorders of pregnancy refers to PET, HELLP, Imminent eclampsia, PIH and chronic HT. Placental abnormalities refers to placental insufficiency, abruptio placentae, placenta previa, placenta accreta and chorioamnionitis. Abnormal labour refers to failed IOL, poor progress of labour, PROM, prolonged labour.
Bold values indicate statistical significance.

TABLE 3 Characteristics of neonates enrolled in study.

Neonatal Characteristics	All n/N (%)	Hypothermic n/N (%)	Normothermic n/N (%)	p-value	Odds-ratio (95% CI)
Gestational age* (weeks)	37.1 ± 3.54	37.0 ± 3.62	37.2 ± 3.48	0.347	0.98 (0.95–1.02)
Birth weight (g)*	2766.4 ± 796.1	2749.5 ± 833.3	2778.3 ± 769.3	0.570	0.99 (0.99–1.00)
Season of birth (Winter)	267/1,017 (26.3)	122/421 (29.0)	145/596 (24.3)	0.207	1.08 (0.96–1.21)
Meconium exposure	169/772 (21.9)	59/325 (18.2)	110/447 (24.6)	0.033	0.68 (0.48–0.99)
Received resuscitation	171/913 (18.7)	98/534 (18.4)	73/379 (19.2)	0.729	1.06 (0.76–1.49)
APGAR 1 (<7)	196/1,009 (19.4)	87/417 (20.9)	109/592 (18.4)	0.589	1.60 (0.91–2.81)

*Mean ± SD.
Missing values: sex ($n = 83$), race ($n = 18$), Gestational age ($n = 41$), meconium exposure ($n = 245$), APGAR 1 ($n = 8$), APGAR 5 ($n = 14$), APGAR 10 ($n = 530$), birth weight ($n = 6$), resuscitation ($n = 104$). Bold values indicate statistical significance.

($n = 8$) had a cardiac pathology, 1.0% ($n = 10$) had a congenital anomaly, 0.3% ($n = 3$) had subarachnoid haemorrhages and 2.0% ($n = 20$) were admitted for weight gain (**Table 6**). Neonates with hypothermia were less likely to have respiratory pathology (36.1% vs. 42.3%; p-0.047). **Table 6**. Thirty-one percent of ($n = 299$) neonates required admission, whereas 68% ($n = 652$) were discharged (**Table 7**). Only 0.2% ($n = 2$) neonates demised, 1 of which was hypothermic. It is believed that both deaths were stillbirths as their APGAR scores at 1 min were both 0.

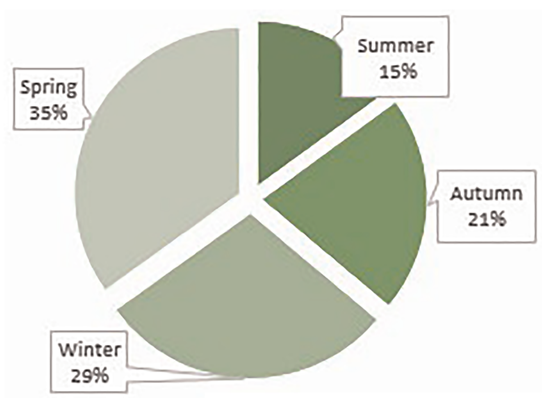

FIGURE 3
Seasonal variation amongst hypothermic neonates.

Factors associated with hypothermia

Having had CPR, respiratory pathology, and an elevated lactate were associated with hypothermia. In the multivariate logistic

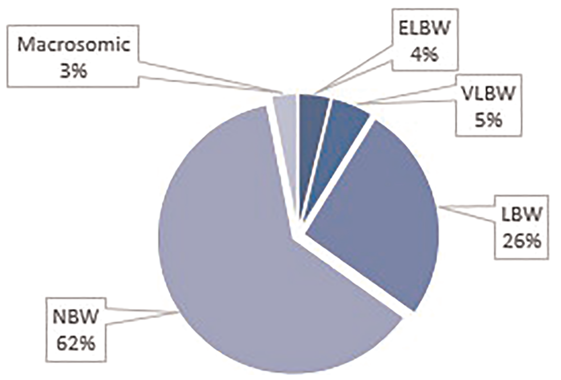

FIGURE 4
Weight distribution amongst hypothermic neonates.

regression model, neonates who were hypothermic were more likely to have an elevated lactate. (**Table 8**). Maternal factors were not found to significantly contribute to neonatal hypothermia.

Discussion

Most of the hypothermic patients in our cohort had mild hypothermia. Incidence of hypothermia in our study population and those neonates admitted were generally comparable. Neonates who were moderately and severely hypothermic had higher admission rates though this was not significant.

Only a small number of neonates required an arterial blood gas, with neonates who were hypothermic being more likely to have an elevated serum lactate. Elevated serum lactate results from

TABLE 4 Resuscitative measures undertaken.

Resuscitation details	All $N = 913$ n (%)	Hypothermic $N = 379$ n (%)	Normothermic $N = 534$ n (%)	p-value	Odds-ratio (95% CI)
BMV only	151 (16.5)	60 (15.8)	91 (5.5)	0.628	0.92 (0.64–1.31)
BMV and CPR	20 (2.2)	13 (3.4)	7 (0.7)	0.031	2.67 (1.06–6.77)
BMV, CPR and intubation	5 (0.5)	4 (1.1)	1 (0.1)	0.080	5.70 (0.63–51.07)
BMV, CPR, intubation and adrenaline	3 (0.3)	2 (0.5)	1 (0.1)	0.376	2.83 (0.26–31.10)

Missing ($n = 104$) BMV – bag mask ventilation, CPR – cardiopulmonary resuscitationBold values indicate statistical significance.

TABLE 5 Neonatal biochemical parameters.

Neonatal Biochemical Factors	All Median (IQR)	Hypothermic Median (IQR)	Normothermic Median (IQR)	p-value	Odds- ratio (95% CI)
pH	7.26 (7.18–7.34)	7.24 (7.05–7.34)	7.26 (7.20–7.36)	0.54	0.26 (0.01–5.24)
pCO2	37.9 (29.2–48.0)	37.4 (29.2–53.2)	38.5 (29.6–42.8)	0.37	1.03 (1.00–1.06)
pO2*	107.2 (84.0–132.0)	107.4 (61.4–166.0)	111.0 (86.8–129.0)	0.98	1.00 (0.99–1.01)
Lactate	4.9 (2.5–15.0)	13.3 (5.4–19.7)	3.2 (1.9–5.1)	0.007	1.13 (1.01–1.26)
Base excess*	−8.2 ± 8.8	−9.5 ± 11.6	−7.3 ± 6.1	0.37	0.97 (0.91–1.04)

*Mean and Standard deviation values rather than median and IQR. Neonates that had arterial blood gases drawn: pH ($n = 54$), pCO2 ($n = 56$), pO2 ($n = 54$), base excess ($n = 52$), lactate ($n = 33$).
Bold values indicate statistical significance odds ratio results.

TABLE 6 Neonatal diagnoses among study participants.

Neonatal diagnosis	All $N = 1,017$ n (%)	Hypothermic $N = 421$ n (%)	Normothermic $N = 596$ n (%)	p-value	Odds-ratio (95% CI)
Respiratory	404 (39.7)	152 (36.1)	252 (42.3)	0.047	0.77 (0.597–0.997)
Asphyxia	25 (2.5)	12 (2.9)	13 (2.2)	0.497	1.32 (0.59–2.91)
Cardiac	8 (0.8)	5 (1.2)	3 (0.5)	0.224	2.38 (0.56–1.00)
Congenital anomaly	10 (1.0)	3 (0.7)	7 (1.2)	0.462	0.60 (0.16–2.35)
Subarachnoid haemorrhage	3 (0.3)	1 (0.2)	2 (0.3)	0.776	0.71 (0.06–7.82)
Weight gain	20 (2.0)	8 (1.9)	12 (2.0)	0.898	0.94 (0.38–2.32)

Bold values indicate statistical significance odds ratio results.

TABLE 7 Neonatal outcomes among study participants.

Neonatal outcome	All *N* = 953 *n* (%)	Hypothermic *N* = 401 *n*/*N* (%)	Normothermic *N* = 552 *n* (%)	*p*-value	Odds-ratio (95% CI)
Neonatal outcome				0.953	1.02 (0.78–1.34)
Admit	299 (31.4)	125 (31.2)	174 (31.5)		
Discharged	652 (68.4)	275 (68.6)	377 (68.3)		
Death	2 (0.2)	1 (0.2)	1 (0.2)		

Missing (*n* = 64).

TABLE 8 Factors associated with neonatal hypothermia.

Factors associated with hypothermia	Unadjusted Odds-ratio (95% CI)	*p*-value	Adjusted Odds-ratio (95% CI)	*p*-value
Meconium exposure	0.68 (0.48–0.99)	0.033	–	–
Respiratory pathology	0.77 (0.597–0.997)	0.048	4.35 (0.418–45.3)	0.219
BMV and CPR	2.67 (1.06–6.77)	0.038	0.409 (0.45–3.67)	0.425
Lactate	1.13 (1.01–1.26)	0.032	1.17 (1.02–1.34)	0.024

Variables with few observations were excluded from the multivariable regression model.
Variables with a *p*-values <0.1 were used to build the multivariate regression model.
The meconium aspiration variable was omitted from the linear regression due to no observations in the non-hypothermia group.
BMV- bag mask ventilation, CPR – cardiopulmonary resuscitation.

anaerobic respiration, when oxygen demand is higher than the oxygen supply that the body is receiving. Therefore, low body temperature may reflect thermoregulatory failure due to insufficient energy secondary to a lack of oxygen or metabolite (5). Of the 13 neonates with elevated lactate and hypothermia, 11 had an APGAR score at 1 min less than 7 (84.6%). Hence, they received resuscitation and therefore had an element of encephalopathy; however, only 2 met the definition for intrapartum asphyxia; as the other neonates improved their APGAR scores at 5 min after resuscitation. Lactate takes longer than pH to normalize (6). Our study design did not allow for ascribing causation between hypothermia and higher lactate levels but the association is interesting to note.

Neonates who were hypothermic were more likely to have an elevated lactate. Hypothermia may be associated with hypoxia, poor perfusion and metabolic acidosis (2). This causes a build up of lactate in hypothermic neonates. In the current study hypothermic neonates were not hypoxic but had a metabolic acidosis which was not significant. Other causes of a high lactate would need to be investigated.

BMV together with CPR as a means of resuscitation at birth was also associated with hypothermia ($p = 0.031$). A possible explanation for this could be that during emergency resuscitations, neonates were exposed for adequate chest compressions to be delivered. This finding is similar to a study done in Bangladesh (OR = 2.43) (7) and a study done in Iran (OR = 1.91) (8).

Patients with respiratory pathology are closely monitored, as they often go on to require ventilation and admission to ICU. For this reason, it is believed that they were found to be less hypothermic in this study as they were likely kept warmer as a general measure. A study in Denmark found that neonates with hypothermia had an increase odds of having respiratory distress syndrome and bronchopulmonary dysplasia, however when these results were adjusted for confounders the findings were not significant (9). Complications of respiratory distress syndrome, need for respiratory support and an increase in admission to the NICU or standard care nursery are seen with a higher prevalence in neonates who are hypothermic (10, 11).

Studies have shown that neonates who are small for gestational age or low birthweight are more prone to hypothermia. Reasons cited for this are large head to body surface area and decreased insulation due to decreased body fat (10). Surprisingly neonates with IUGR were less likely to be hypothermic in this study although the group sizes for this comparison were very small. Merazzi et al. reported similar findings; where low birth weight neonates (< 2500 g) was not significantly associated with hypothermia and suggest that birth weight has a smaller effect on body temperature in healthy term and late preterm neonates (11). Heat loss in neonates occurs *via* 4 mechanisms which includes evaporation. Transepidermal water loss (TEWL) is inversely proportional to the gestational age with low TEWL in term neonates. Preterm neonates who are SGA have lower TEWL than preterm neonates who are appropriate for gestational age (12). Neonates with IUGR have a more developed dermis and epidermis and may be more equipped to maintain homeostasis as the skin barrier may be fully developed. We hypothesize that IUGR neonates have more mature skin and less subcutaneous fat and are thus less likely to lose heat *via*

TEWL. The number of IUGR neonates are quite small in this study, thus it is difficult to make meaningful conclusions. Further studies are required to elucidate this hypothesis.

This study also evaluated the common factors known to be associated with neonatal hypothermia such as low birth weight, prematurity and season in which the neonate was born. In this study most neonates had a normal birth weight and were not premature. This could be due to the sample population selected as a high proportion of neonates who were born *via* Caesarean section were term neonates. Neonates in this study were mostly born in spring followed by winter. This could be explained by a seasonal variation in the number of deliveries with a higher proportion of neonates born in spring and winter, thus giving a relatively higher proportion of neonates being hypothermic. In addition, spring temperatures in Johannesburg can be as low as 8 to 12 °C (13).

The limitations of the study include the retrospective study design and missing variables. Thus, the study was not powered to fully elucidate the associated factors of hypothermia. The time at which temperatures was taken were not documented. Given that sicker neonates were more likely to have an ABG drawn, this lends itself to a selection bias in terms of the biochemical parameters documented.

Conclusion

Hypothermia is a significant contributor to morbidity and mortality in many settings and mild hypothermia is often prevalent in the setting of Caesarean delivery. Receiving CPR and having an elevated lactate was associated with hypothermia in this cohort. During resuscitation more concerted efforts should be put in to place to prevent hypothermia. There is a need for future studies investigating hypothermia in neonates born *via* Caesarean section including a non-Caesarean section control group.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee [HREC] (Medical) of the University of the Witwatersrand. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors have contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Ashish KC,
Uppsala University, Sweden

REVIEWED BY
Jessica Duby,
McGill University Health Centre, Canada
Getaye Worku Tesema,
Debre Berhan University, Ethiopia

*CORRESPONDENCE
Rashidul Azad
rashidul.azad@icddrb.org,
rashedazad123@gmail.com

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Mother's care-seeking behavior for neonatal danger signs from qualified providers in rural Bangladesh: A generalized structural equation modeling and mediation analysis

Rashidul Azad[1]*, Sk Masum Billah[1,2], Bal Ram Bhui[3], Nazia Binte Ali[1,4], Samantha Herrera[5], Joseph de Graft-Johnson[6], Lyndsey Garg[6], Sabrina Sharmin Priyanka[1], Shams Zubair[3], S. M. Rokonuzzaman[1], Mohammad Mahmoodur Rahman[1], Umme Salma Jahan Meena[3] and Shams El Arifeen[1]

[1]International Centre for Diarrhoeal Disease Research, Bangladesh (Icddr,b), Dhaka, Bangladesh, [2]The University of Sydney School of Public Health, Sydney, NSW, Australia, [3]Save the Children, Dhaka, Bangladesh, [4]Harvard T.H. Chan School of Public Health, Boston, United States, [5]PATH, Washington, DC, United States, [6]Save the Children, Washington, DC, United States

Background: Neonatal deaths contribute to nearly half (47%) of under-five mortality globally and 67% in Bangladesh. Despite high neonatal mortality, care-seeking from qualified providers for newborn danger signs remains low. Identification of direct and indirect factors and their pathways affecting care-seeking will help to design a well-targeted intervention. This study assessed the direct, indirect, and total effect of the predictive factors on neonatal care-seeking in Bangladesh.

Materials and methods: This was a cross-sectional baseline household survey conducted in 14 districts of Bangladesh in 2019 with 17,251 recently delivered women (RDW) with a live birth outcome in the preceding 15 months. We used a two-stage stratified cluster sampling process to select the samples from 14 districts. We investigated the inter-relationship of maternal background characteristics, maternal health utilizations, child/neonate factors, health service delivery-related factors and newborn danger sign knowledge with newborn care-seeking practices and estimated the direct, indirect, and total effects using Generalized Structural Equation Modeling (GSEM) and mediation analysis. p-value = 0.05 was considered statistically significant. The result of the mediation analysis was reported in Log Odds (LOD). The positive LOD (LOD > 0) implies a positive association.

Results: Half of the mothers (50.8%) reported a neonatal illness and among them, only 36.5% mothers of sick neonates sought care from qualified providers. Our mediation analysis showed that maternal health utilization factors, i.e., 4 + antenatal care visits (ANC) from a qualified provider (LOD: 0.63, 95% CI: 0.49, 0.78), facility delivery (LOD: 0.74, 95% CI: 0.30, 1.17) and postnatal care (PNC) from a qualified provider (LOD: 0.50, 95% CI: 0.21, 0.78) showed the highest total effect over other factors domains, and therefore, were the most important modifiable predictors for qualified neonatal care-seeking. Other important factors that directly and/or indirectly increased the chance of newborn care-seeking from qualified providers were household wealth (LOD: 0.86, 95% CI: 0.70, 1.02), maternal education (LOD: 0.48, 95% CI: 0.32, 0.63), distance to nearest health facility (LOD: 0.20, 95% CI: 0.10, 0.30), community health worker's (CHWs) home visits during ANC (LOD: 0.24, 95% CI: 0.13, 0.36), neonatal danger sign counseling after delivery (LOD: 0.20, 95% CI: 0.06, 0.34) and women's knowledge of neonatal danger signs (LOD: 0.37, 95% CI: 0.09, 0.64).

Conclusion: The inter-relationship and highest summative effect of ANC, facility delivery, and PNC on newborn care-seeking suggested the maternal care continuum altogether from ANC to facility delivery and PNC to improve care-seeking for the sick newborn. Additionally, referral training for unqualified providers, targeted intervention for poorer households, increasing CHWs home visits and neonatal danger sign counseling at the facility and community should also be considered.

KEYWORDS

care-seeking behavior, neonatal danger signs, neonatal illness, newborn illness, Bangladesh, generalized structural equation modeling (GSEM), mediation analysis

Introduction

Globally, tremendous progress in child survival has been made over the last three decades. Under-five child deaths decreased by 58 percent between 1990 and 2018, from 12.5 million to 5.3 million. Almost half (2.5 million) of these deaths were classified as neonatal deaths, occurring in the first 28 days of life, showing the high burden of child mortality at this early age (1).

Neonatal mortality varies greatly across geographical regions and is mostly concentrated in low and middle-income countries. In Sub-Saharan Africa and Southern Asia, the average neonatal mortality rate (NMR) ranges between 25 and 28 per 1,000 live births, whereas in Europe, Northern America, Oceania, and Eastern Asia the NMR ranges between 2 and 4 per 1,000 live births (1). In Southern Asia, between 2015 and 2018, almost 1 million newborns died each year, with the neonatal death proportion among under-five child death increasing from 46% in 1990 to 62% in 2018, which is the highest proportion of deaths in South Asia compared to other regions of the world (1). For Bangladesh, NMR has increased to 30 in 2018 from 28 in 2014; which led to an increase of neonatal death proportion among under-five child deaths from 61% to 67% during the same period (2, 3).

A neonatal death surveillance in four districts of Bangladesh in 2016 reported that the leading cause of neonatal death was birth asphyxia (43%), followed by infections (29.3%), and prematurity (22.2%). Day-wise disaggregation showed that 63.4% of newborns who died on their birthday died due to asphyxia, whereas infections were the main cause of neonatal deaths among newborns who died between days 1–6 (48.8%) and days 7–28 (57.5%) (4). Other studies in Bangladesh and similar contexts reported similar causes and trends (5–7). Early identification, treatment and/or referral of these major causes of newborn deaths are essential to reduce neonatal deaths, especially infections, which are better managed by a qualified provider when identified and referred early (8–10).

In low and middle-income countries (LMICs), several interventions implemented around the time of birth have been proven effective in reducing neonatal mortality. These interventions are delivered through an integrated community and health facility platform (8, 11, 12). Domiciliary services by health workers' home visits, birth preparedness education, newborn care practices, identification of newborn danger signs, and early care-seeking have been proven effective to reduce neonatal mortality (8, 11–14). However, caregivers' timely identification of neonatal danger signs and subsequent care-seeking from qualified health providers should be the core of a successful healthcare intervention for neonatal survival (14).

Care-seeking behavior for sick newborns remains low and is a key challenge to reduce neonatal deaths in LMICs (14). This is further compounded by slow recognition of danger signs and delayed care-seeking, as the health condition of sick newborns declines rapidly and can quickly progress to death (15, 16). Care-seeking behavior is a complex decision-making process (17). Multiple factors (i.e., illness severity perception, maternal and newborn factors, health care utilization practices, socio-economic and cultural factors, geographical location, quality of care, cost of care, etc.) influence the caregivers' and family members' care-seeking behavior for neonatal illness (14, 18–21).

In-depth understanding of care-seeking behaviors for newborns with danger signs would help to design effective interventions at both community and facility levels (19, 22). There are limited data and studies on newborn illness care-seeking practices in Bangladesh. Earlier studies in Bangladesh investigated the direct relationship of predictor variables with care-seeking practices but did not explore the inter-relationship among the predictor variables (21, 23–26). The most important or influential predictor variables on neonatal care-seeking behavior can be identified through analysis of the inter-relationships among predictor variables and their association with the main outcome variable. This nuanced understanding of important predictors of care-seeking can be used by policy makers, program managers and researchers to inform the design and testing of interventions to improve care-seeking behavior for sick newborns.

Structural Equation Modeling (SEM) has been widely used to simultaneously estimate and test the effects of variables and their inter-relationships within the complex hypothetical conceptual framework (27–30). It allows identification of the pathways of cause and effect from distal factors to proximate factors and to the outcome of interest. Generalized Structural Equation Modeling (GSEM) is the extended and generalized form of SEM for the estimation and testing the effects of categorical, continuous and count variables (31). We used GSEM to explain the relationships among predictor variables in determining mothers' care-seeking behavior. We also conducted a mediation analysis to estimate the direct, indirect (mediated), and total effects of predictors on the main outcome among each possible mediated pathway found significant in the GSEM analysis (32, 33).

We include the description of the hypothesized conceptual/theoretical model of the inter-relationships between the predictors and the neonatal care-seeking outcome in the next section. Our research objective is to examine this hypothetical inter-relationship with GSEM and identify the most important predictors that have both direct and indirect relationships among them and with the outcome variable. We also estimated the direct, indirect (mediated), and total effect of the predictor variables on neonatal care-seeking.

Materials and methods

Study design, setting, source population and study population

This was a population-based cross-sectional baseline survey conducted in 14 districts (Noakhali, Feni, Chandpur, Lakshmipur, Brahmanbaria, Habiganj, Manikganj, Faridpur, Madaripur, Kushtia, Kishoreganj, Natore, Rajbari and Bhola) that are part of the evaluation of MaMoni Maternal and Newborn Care Strengthening Project (MNCSP) and included both intervention and comparison districts. The MaMoni MNCSP project was implemented in 10 intervention districts out of 64 districts in Bangladesh. MaMoni MNCSP was a United States Agency for International Development-funded project (2018–2023) focused on strengthening public sector maternal and newborn care (MNC) services through increased and equitable accessibility and utilization of quality MNC services in Bangladesh. The key intermediary objectives of MaMoni MNCSP were to advance health system responsiveness, improve MNC service quality and governance, access and demand for services and healthy household practices, and strengthen national capacity to deliver these services with quality at scale. MaMoni MNCSP was implemented by a consortium of local and international partners led by Save the Children. Details of project interventions, project evaluation design, and study settings are available elsewhere (35). As a MaMoni project consortium member, icddr,b conducted the cross-sectional baseline household survey to measure population level coverage of key maternal and newborn practice indicators. The source population was the recently delivered women (RDW) who gave birth within the last 15 months irrespective of birth outcome status in the above-mentioned 14 districts. The study population of RDW was selected from the source population with the sampling techniques described below.

Sample size, sampling and study subjects

The sample size was primarily calculated to detect the minimum difference between intervention and comparison districts considering neonatal mortality as the main outcome of the MaMoni MNCSP evaluation study. The neonatal mortality rate was 38 per 1,000 life birth (2) and during the sample size calculation; we assumed a 25% reduction of neonatal mortality as per the intervention effect. Considering 2.5:1 intervention to comparison samples size ratio, 80% power, 5% level of significance, 1.5 design effect, and 5% non-response, the calculated sample size was 16,654 in total (11,896 in intervention districts and 4,758 in comparison districts). Secondarily, we also calculated the sample size to estimate the district level coverage of public health facility delivery. Considering 14.3% of public facility delivery prevalence (2), 2.5% absolute precision, 5% non-response and 1.5 design effect, the calculated sample size for each district was ≅1200. So, the total sample size for the 14 evaluation districts was 16,800.

We followed a two-stage stratified cluster sampling process for selecting 1,200 samples from each district. We selected 120

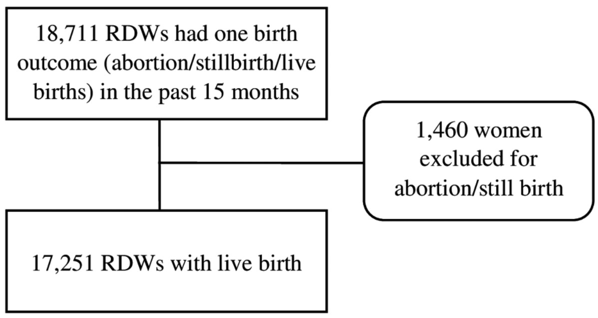


FIGURE 1
Selection of the sample for the analysis.

clusters per district and each cluster needed to comprise 10 samples (RDW). Considering the average household size 4.4 and crude birth rate of 21.0 per 1,000 population per year (2), we needed to list at least 120 households to attain ~10 samples. We conducted the village level clustering and followed the Probability proportional to size (PPS) sampling for the selection of cluster/village within each district. Considering the time and cost involved in a complete listing of households of villages, the project decided not to do a complete listing of all households in each selected village. Alternatively, we selected a section of a village with 120 households. Therefore, we needed a starting point to start listing 120 households for each cluster within the selected village. We used the eligible couple registers maintained by the Family Welfare Assistants (FWA) to randomly select the starting household (index household) to determine starting household. From that index household, we continued till we reach 120 households to complete one cluster. From each cluster we expected to find 10 RDW samples; however, if there were more RDWs we interviewed all.

A total of 18,711 RDW having at least one birth outcome (abortion/stillbirth/live birth) in the past 15 months were interviewed as the study population in the survey. For the analysis, 1,460 women were excluded who experienced an abortion or a stillbirth and included 17,251 RDW with live birth as the study subject. If a woman had twin births, then the last child's information on neonatal complications and care-seeking behavior was collected. **Figure 1** shows the study participant selection for the analysis of this paper.

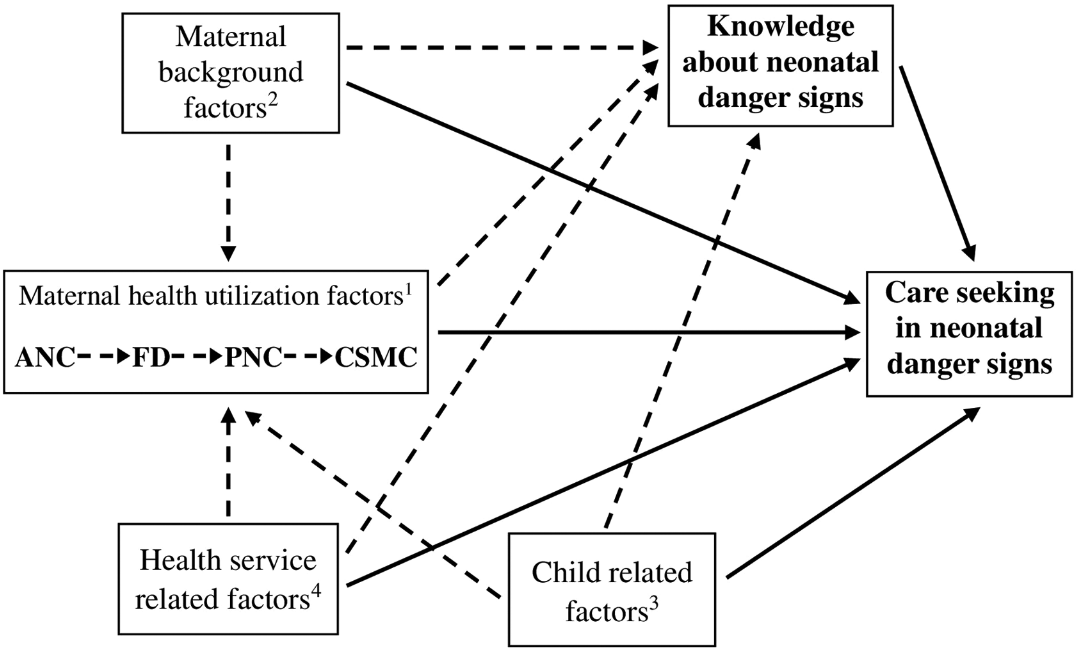
Data collection and quality control

The data collection instrument was adapted from the Bangladesh Demographic and Health Survey (BDHS) questionnaire (2, 3). The study investigators pre-tested the adapted questionnaire before data collection. We have prepared the tools in both English and Bangla. However, all interviews were conducted in the Bangla language only. The interview questionnaire included information on socio-demographic characteristics of the households, women's background characteristics, childbirth history, health service-related information, maternal health care practices, child's experience of complications, and care-seeking behaviors for sick neonates. We recruited data collectors and supervisors who had extensive experience in survey data collection and most of them had an undergraduate degree in social science. The data collection team comprised 2 field research officers (FRO), 7 field research supervisors (FRS), and 56 data collectors (DC). Each small data collection team consisted of 1 FRS and 8 DC, deployed for the data collection of 2 districts. The FROs supervised all small teams by visiting the team sequentially. All data collectors and supervisors received training on the data collection tools before the start of data collection. Data collection was carried out from April to September 2019. Data was collected on electronic devices, with built-in skips and immediate identification of erroneous entry was built in to improve data quality at the time of entry. FRO and FRS accompanied the DC during data collection. Supervisors organized regular team meetings for supervisory feedback, data rechecking and discussing data collection issues. A quality control (QC) team comprised of interviewers and field-based supervisors monitored and ensured data integrity by re-interviewing and matching with original data. The QC team re-interviewed approximately 3% of the total interviews.

Hypothesized conceptual/theoretical model

Our hypothesized inter-relationship among predictors and main outcome variables was built based on an extensive literature review and the plausibility of inter-relationships (**Figure 2**). Lines indicate the relationships and direction of relationships between the variables. The lack of a line implies no hypothesized relationship between the variables (34). The variables identified as predictors of care-seeking behaviors for neonatal danger signs were placed into five groups/domains: (1) maternal background characteristics, (2) maternal health care utilization factors, (3) child-related factors, (4) health service-related factors and (5) knowledge on neonatal danger signs. The hypothesized predictors of each domain and scientific evidence used to construct the theoretical model are included in the **Supplementary Information S1**.

Relationships between factors and the main outcome variable are characterized as either direct or indirect relationships. A solid line indicates a direct relationship between the predictor and care-seeking behavior. Whereas, an indirect relationship, that is the mediated relationship through a second predictor variable (called a mediator variable), is represented by the dotted line.



[1]**Maternal health care utilization factors:** ANC=Antenatal care, FD=Facility delivery, PNC= Postnatal care, CSMC=Care-seeking in maternal complication;
[2]**Maternal background factors:** Maternal age, education and wealth quintile;
[3]**Child related factors:** Neonate's sex, history of child mortality and number of living children;
[4]**Health service related factors:** Distance of health center, home visit of community health workers (CHWs) during pregnancy period and provision of neonatal danger sign counseling after delivery

FIGURE 2
Hypothetical inter-relationship of different factors associated with care-seeking for neonatal danger signs.

The following **Figure 3** is demonstrating the hypothesized direct and indirect effects through mediated pathways for the household wealth and ANC utilization variables. As with **Figure 2**, the solid represents the direct effect and the dotted arrows show the indirect effects through the mediators.

Study variables

Endogenous variables

In the structural equation model, some variables could be simultaneously used as the independent and dependent variables or only the dependent variable. These variables are called endogenous variables. In our GSEM model, six simultaneous multivariable equations of six endogenous/dependent variables were used. The six interrelated endogenous variables were care-seeking for sick neonates from qualified providers, woman's knowledge of neonatal danger signs, care-seeking for last maternal complication from qualified providers, PNC from qualified providers, facility delivery, and attendance of four or more ANC visits from qualified providers. Medical doctors, nurses, midwives, paramedics, family welfare visitors, medical assistants, sub-assistant community medical officers, and community skilled birth attendants were considered qualified providers (2, 3). Maternal complications were defined as any severe headaches with blurry vision, convulsions, high blood pressure, excessive vaginal bleeding, prolonged labor, body parts except the head coming out first, placenta remaining inside, foul-smelling discharge with high fever, and oedema during pregnancy/delivery/after the delivery period. Knowledge of neonatal danger signs was measured as the number of danger signs for which care should be sought. The interview question consisted of 22 danger sign options, which included difficulty or fast breathing, pneumonia, cold/cough, low temperature, high temperature, yellow skin/eye, poor sucking or feeding, discharge from the umbilical cord, skin lesions/blisters, red or swollen eyes with pus, skin rash, measles, convulsions/spasms/rigidity, lethargy/unconsciousness, baby doesn't cry, doesn't pass urine, doesn't pass stool, continuous vomiting, distended abdomen, difficult to wake, diarrhea, and chest in-drawing. Interviewers did not read out the danger signs options while asking this question. For the following question, interviewers read out all the above mentioned danger signs and asked the women whether the child experienced any of these danger

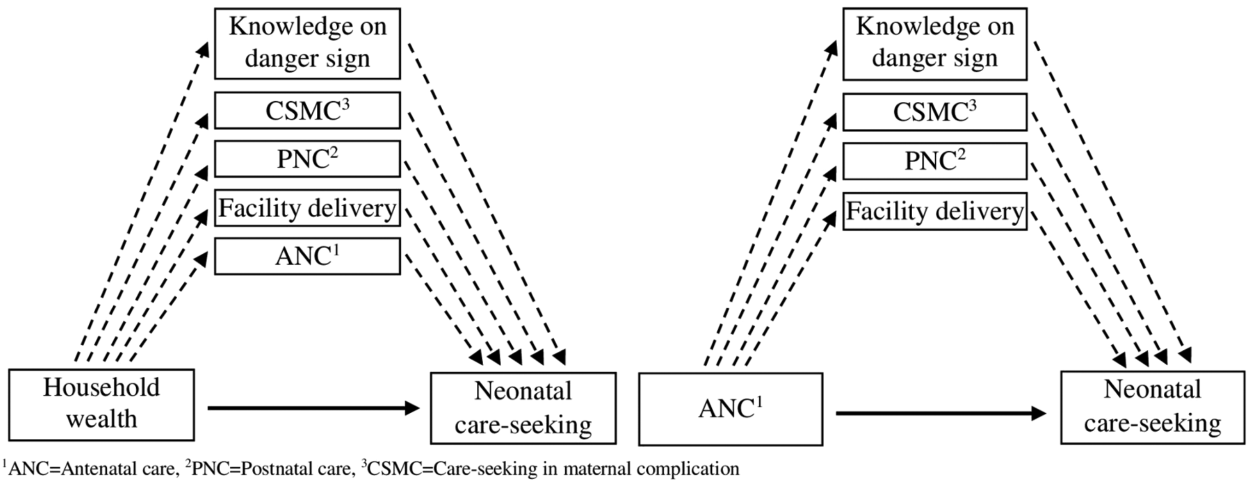


FIGURE 3
Direct and indirect effect pathway from household wealth and ANC to neonatal care-seeking.

signs. Then the subsequent care-seeking behavior was asked. As endogenous variable neonatal danger sign knowledge was used as a continuous variable. All the other endogenous variables were binomial, categorized as yes or no.

Exogenous variables

All the variables used only as independent variables in the structural model are called exogenous variables. The exogenous variables included in the model were maternal age, education, wealth quintile, the total number of live children, history of child death, sex of newborn, distance to the nearest health facility, facility delivery, home visit by a community health worker (CHW) during the pregnancy period, and receipt of any counseling on neonatal danger signs after delivery. We categorized the distance to the nearest health facility into two categories (<5 km and 5 km or more) and operationally defined "<5 km" as the near distance and "5 km and more" as the long distance (2, 3). For the construction of the household wealth quintile, we used household assets, construction materials of household (roof, walls, and floor), source of drinking water, toilet type, number of rooms in the household, ownership of homestead and agricultural land, ownership of domestic animals (cattle, goat, and chicken) and type of fuel used for cooking. For the exogenous variable on women's knowledge of neonatal danger signs, it was categorized into three categories (0, 1–4, and 5+). We operationally defined the danger sign knowledge of less than 5 as low knowledge of newborn danger signs (86). Consistent with other similar literature, the standard category of other exogenous variables was used in the structured equation model (9, 21, 23, 26, 40–42).

Data analysis

First, we did a descriptive summary of all maternal background characteristics, child-related factors, health service-related factors, and all maternal and child health utilization factors. The descriptive analysis was also done among healthy neonates and sick neonates. Then, we used GSEM in the subpopulation of sick neonates ($N = 8765$) to estimate the inter-relationships of the predictor variables and newborn care-seeking. In our GSEM model, we used the Bernoulli family and logit link function for binary endogenous variables (4 + ANC from qualified providers, facility delivery, PNC from qualified providers, care-seeking of maternal complication, and care-seeking of sick neonates) and gaussian family and identity link function for the continuous endogenous variable (knowledge on neonatal danger signs) (36). Additionally, the robust standard error was considered as mitigation of the multivariate normality (MVN) assumption (37). The indirect (mediated) effect of each indirect pathway of each mediator was calculated with multiplicated coefficients. The total indirect effect of the variable was estimated by the sum of multiplicated coefficients of all mediated pathways. The total effect of each indicator was calculated as a sum of the direct and total indirect effects. These indirect, direct, and total effects were obtained using the "nlcom" post-estimation command after the GSEM model. All the indirect, direct, and total effects were estimated and reported in terms of Log Odds (LOD), which has the linear additive property. Using LOD calculation of mediating proportion and cross-comparison of effect can be made. The mediation proportion was calculated by dividing the indirect over the total effect (38). Due to the comparability of effects across the predictors, the average relative effect was calculated for the multi-categorical independent variable (39). As a supplementary analysis, we also conducted the distribution of very severe neonatal complications according to neonate's sex (**Supplementary Table S1**) and the care-seeking distribution of qualified and unqualified providers according to reported very severe complications (**Supplementary Table S2**). All data analysis was conducted in STATA, version 14.0.

Ethical consideration

Ethical approval was granted by the Ethical Review Committee of Save the Children USA and the Institutional Review Board (IRB) of icddr,b (Protocol number: PR#18099). Informed written consent was obtained from the study participants after explaining the purpose of the data collection, methods and procedure, use of data, risks, benefits, principle of no compensation, measures for privacy and confidentiality, their voluntary participation, and right to withdraw from the study at any time without showing any cause. For mothers below 18 years, we also took informed written consent from a legal guardian or next of kin.

Results

Description of study participants

The majority of mothers were between 20 and 34 years of age (76.9%) and 15.2% of mothers were less than 20 years. About 7.3% of mothers had no education, 12.5% stopped school before completing primary education, and only 21.3% completed secondary or higher levels of study. Overall, 34.7% of mothers reported that this was their first child and 10% experienced a child death in the past.

Overall, less than one-third (27.3%) of mothers received four or more ANC visits from qualified providers during their last pregnancy, around half (52.2%) gave birth in a health facility, 43.4% received PNC from qualified providers, and 65.0% sought care from qualified providers during their most recent maternal complication ($N = 4713$). Mothers' knowledge of neonatal danger signs was low. Out of 22 neonatal danger signs, 3.3% of mothers of sick neonates had no knowledge of any neonatal danger sign, 76.4% knew 1–4 danger signs and only 20.3% of mothers knew 5 or more danger signs (**Table 1**).

Among all mothers, 8,765 mothers (50.8%) reported that their newborns experienced at least one danger sign in the first month of life. Among the mothers of those sick neonates, almost all (94.4%) sought care from any type of provider, however, only about one-third (36.5%) sought care from a qualified provider (**Table 1**). Among severe neonatal danger signs, care-seeking from qualified providers was high for difficult or fast breathing (45.4%), chest in-drawing (50.0%), and fever (43.8%) (**Supplementary Table S2**).

Identification of direct and indirect predictors and effect pathways on newborn care-seeking

Table 2 details the inter-relationship among maternal health utilization indicators, neonatal danger sign knowledge, maternal background characteristics, child/neonate-related factors, and health service-related factors to explain neonatal care-seeking behavior. In the supplementary materials, we have included a table (**Supplementary Table S3**) that summarizes the significant inter-relationships of the GSEM model (**Table 2**), i.e., the significant direct and indirect effect pathway and the effect measures of predictors and mediators on the main outcome variable.

Neonatal care-seeking from a qualified provider was associated with maternal danger sign knowledge. The adjusted odd of neonatal care-seeking behavior was higher among mothers with knowledge of 5 or more neonatal danger signs compared to mothers with no knowledge of neonatal danger signs (AOR: 1.44, 95% CI: 1.09, 1.90). Neonatal care-seeking behavior was not directly associated with maternal care-seeking behavior during complications (AOR: 1.06, 95% CI: 0.96, 1.18).

Three maternal health care utilization indicators (PNC from a qualified provider, facility delivery, and 4 + ANC from a qualified provider) were both directly and indirectly associated with neonatal care-seeking behavior. Mothers who received a PNC visit from a qualified provider were slightly more likely to seek care when their newborn exhibited danger signs (AOR: 1.18, 95% CI: 1.03, 1.34). In addition, maternal PNC also mediated the newborn care-seeking indirectly by increasing the knowledge of neonatal danger signs greatly (Aβ: 0.46, 95% CI: 0.35, 0.57). Among the maternal health utilization factors, health facility delivery directly increased the adjusted odds of care-seeking for neonatal illness (AOR: 1.30, 95% CI: 1.14, 1.48) and indirectly mediated the care-seeking by increasing the odds of receiving a maternal PNC visit (AOR: 41.22, 95% CI: 35.56, 47.77). On the other hand, attending 4 + ANC visits during pregnancy directly increased the odds of neonatal care-seeking behavior of mothers (AOR: 1.26, 95% CI: 1.14, 1.40) and indirectly increased the odds of neonatal care-seeking through increasing the likelihood of receiving a maternal PNC visit (AOR: 1.46, 95% CI: 1.27, 1.68), facility delivery (AOR: 2.53, 95% CI: 2.27, 2.83) and knowledge of neonatal danger signs (Aβ: 0.24, 95% CI: 0.15, 0.33).

Among the maternal background characteristics, only household wealth was directly associated with neonatal care-seeking. The odds of care-seeking for newborn illness

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TABLE 1 Distribution of overall background characteristics of the respondents, and disaggregated by the healthy and sick neonates.

Indicators (%)	Overall (*N* = 17,251)	Newborn with no reported illness (*N* = 8486)	Newborn with reported illness[a] (*N* = 8765)
	n (%)	*n* (%)	*n* (%)
Mother's age			
<20	2,629 (15.2)	1,281 (15.1)	1,348 (15.4)
20–34	13,263 (76.9)	6,524 (76.9)	6,739 (76.9)
35–49	1,359 (7.9)	681 (8.0)	678 (7.7)
Mother's education			
No education	1,267 (7.3)	696 (8.2)	571 (6.5)
Primary incomplete	2,164 (12.5)	1,074 (12.7)	1,090 (12.4)
Primary complete	2,643 (15.3)	1,364 (16.1)	1,279 (14.6)
Secondary incomplete	7,507 (43.5)	3,567 (42.0)	3,940 (45.0)
Secondary complete or higher	3,670 (21.3)	1,785 (21.0)	1,885 (21.5)
Wealth quintile			
Lowest	3,319 (19.2)	1,638 (19.3)	1,681 (19.2)
Second	3,353 (19.4)	1,666 (19.6)	1,687 (19.2)
Middle	3,473 (20.1)	1,691 (19.9)	1,782 (20.3)
Fourth	3,519 (20.4)	1,696 (20.0)	1,823 (20.8)
Highest	3,587 (20.8)	1,795 (21.2)	1,792 (20.4)
Number of living children			
1	5,992 (34.7)	2,860 (33.7)	3,132 (35.7)
2–3	9,302 (53.9)	4,615 (54.4)	4,687 (53.5)
4+	1,957 (11.3)	1,011 (11.9)	946 (10.8)
History of child mortality			
No	15,524 (90.0)	7,644 (90.1)	7,880 (89.9)
Yes	1,727 (10.0)	842 (9.9)	885 (10.1)
Sex of child			
Female	8,882 (51.5)	4,603 (54.2)	4,279 (48.8)
Male	8,369 (48.5)	3,883 (45.8)	4,486 (51.2)
CHW's home visit during ANC			
No	14,193 (82.3)	7,163 (84.4)	7,030 (80.2)
Yes	3,058 (17.7)	1,323 (15.6)	1,735 (19.8)
Newborn Danger Signs counseling during ANC			
No	16,851 (97.7)	8,303 (97.8)	8,548 (97.5)
Yes	400 (2.3)	183 (2.2)	217 (2.5)
Distance of nearest health facility with delivery care			
≤5 km	8,146 (47.2)	3,980 (46.9)	4,166 (47.5)
5+ km	9,105 (52.8)	4,506 (53.1)	4,599 (52.5)
Neonatal danger sign counseling during PNC period			
No	13,011 (75.4)	6,574 (77.5)	6,437 (73.4)
Yes	4,240 (24.6)	1,912 (22.5)	2,328 (26.6)
4+ANC from qualified providers			
No	12,540 (72.7)	6,360 (74.9)	6,180 (70.5)
Yes	4,711 (27.3)	2,126 (25.1)	2,585 (29.5)
Facility delivery			
No	8,254 (47.8)	4,147 (48.9)	4,107 (46.9)
Yes	8,997 (52.2)	4,339 (51.1)	4,658 (53.1)
PNC from qualified providers			
No	9,765 (56.6)	4,877 (57.5)	4,888 (55.8)
Yes	7,486 (43.4)	3,609 (42.5)	3,877 (44.2)
Care-seeking for recent maternal complication (*N* = 4713)			
No	14,188 (35.0)	7,399 (36.8)	6,789 (34.0)
Yes	3,063 (65.0)	1,087 (63.2)	1,976 (66.0)
Knowledge about the neonatal danger sign			
0	589 (3.4)	301 (3.5)	288 (3.3)
1–4	13,618 (78.9)	6,919 (81.5)	6,699 (76.4)
5+	3,044 (17.6)	1,266 (14.9)	1,778 (20.3)
Care-seeking for neonatal danger sign			
No	—	—	457 (5.2)
Yes	—	—	8,308 (94.8)
Care-seeking of neonatal danger sign by type of providers			
No care-seeking			457 (5.2)
Care-seeking from unqualified providers	—	—	5,110 (58.3)
Care-seeking from qualified providers	—	—	3,198 (36.5)

[a]Neonates reported any of the danger sign in first 30 days of life.

increased with household wealth, mothers from households in the higher wealth quintiles were 1.3–1.5 times more likely to seek care than mothers from households in the lowest wealth

TABLE 2 Analysis of interrelationship among the maternal health utilization factors, maternal background factors, child/neonatal factors, health service factors, neonatal danger sign knowledge and the care-seeking for sick neonates as per hypothetical inter-relationship framework (figure 2) using generalized structural equation modeling (GSEM).

Independent variables	Endogenous/dependent variables in GSEM simultaneous equations					
	4 + ANC from qualified providers	Facility delivery	PNC from qualified providers	Care-seeking for maternal complication	Knowledge on neonatal danger sign	Care-seeking for sick neonates from qualified providers
	(*N* = 8765) AOR[£] (95% CI)	(*N* = 8765) AOR (95% CI)	(*N* = 8765) AOR (95% CI)	(*N* = 2993) AOR (95% CI)	(*N* = 8765) Aβ[¥] (95% CI)	(*N* = 8765) AOR (95% CI)
Neonatal danger sign knowledge						
Knowledge about the neonatal danger sign						
0	—	—	—	—	—	1
1–4	—	—	—	—	—	1.24 (0.96, 1.62)
5+	—	—	—	—	—	1.44* (1.09, 1.90)
Maternal health care utilization related factors						
Care-seeking for recent maternal complication						
No	—	—	—	—	—	1
Yes	—	—	—	—	—	1.06 (0.96, 1.18)
PNC from qualified providers						
No	—	—	—	1	Ref	1
Yes	—	—	—	1.96** (1.58, 2.44)	0.46** (0.35, 0.57)	1.18* (1.03, 1.34)
Facility delivery						
No	—	—	1	1	Ref	1
Yes	—	—	41.22** (35.56, 47.77)	1.67** (1.35, 2.07)	−0.35** (−0.46, −0.24)	1.30** (1.14, 1.48)
4 + ANC from qualified providers						
No	—	1	1	1	Ref	1
Yes	—	2.53** (2.27, 2.83)	1.46** (1.27, 1.68)	1.46** (1.20, 1.76)	0.24** (0.15, 0.33)	1.26** (1.14, 1.40)
Maternal background factors						
Mother's age						
<20	1	1	1	1	Ref	1
20–34	1.24** (1.06, 1.45)	1.25** (1.07, 1.45)	0.99 (0.81, 1.20)	1.29 (1.00, 1.67)	0.21** (0.10, 0.33)	0.91 (0.79, 1.04)
35–49	1.04 (0.79, 1.36)	1.99** (1.56, 2.53)	1.62** (1.15, 2.26)	1.49 (0.99, 2.22)	0.22* (0.03, 0.41)	1.07 (0.85, 1.34)
Mother's education						
No education	1	1	1	1	Ref	1
Primary incomplete	1.18 (0.89, 1.58)	0.94 (0.75, 1.17)	1.68** (1.23, 2.3)	1.05 (0.73, 1.51)	0.11 (−0.05, 0.28)	0.83 (0.66, 1.03)
Primary complete	1.36* (1.03, 1.79)	1.08 (0.86, 1.34)	1.55** (1.14, 2.1)	0.95 (0.66, 1.35)	0.22** (0.06, 0.39)	1.03 (0.83, 1.28)
Secondary incomplete	1.73** (1.33, 2.24)	1.39** (1.14, 1.7)	1.85** (1.40, 2.45)	1.22 (0.87, 1.71)	0.26** (0.11, 0.42)	0.91 (0.75, 1.11)
Secondary complete or higher	2.62** (2.00, 3.45)	1.88** (1.50, 2.35)	2.22** (1.63, 3.02)	1.27 (0.87, 1.86)	0.47** (0.29, 0.64)	0.85 (0.68, 1.05)
Wealth quintile						
Lowest	1	1	1	1	Ref	1

(*continued*)

TABLE 2 Continued

Independent variables	Endogenous/dependent variables in GSEM simultaneous equations					
	4 + ANC from qualified providers	Facility delivery	PNC from qualified providers	Care-seeking for maternal complication	Knowledge on neonatal danger sign	Care-seeking for sick neonates from qualified providers
	($N = 8765$) AOR[£] (95% CI)	($N = 8765$) AOR (95% CI)	($N = 8765$) AOR (95% CI)	($N = 2993$) AOR (95% CI)	($N = 8765$) Aβ[¥] (95% CI)	($N = 8765$) AOR (95% CI)
Second	1.14 (0.95, 1.36)	1.45** (1.25, 1.68)	1.13 (0.92, 1.38)	0.92 (0.71, 1.18)	0.10 (−0.01, 0.22)	1.31** (1.13, 1.52)
Middle	1.30** (1.09, 1.55)	1.90** (1.64, 2.20)	1.11 (0.91, 1.35)	1.15 (0.89, 1.47)	−0.03 (−0.15, 0.08)	1.48** (1.28, 1.73)
Fourth	1.80** (1.52, 2.14)	2.59** (2.22, 3.01)	1.27* (1.04, 1.56)	1.09 (0.84, 1.42)	0.07 (−0.05, 0.19)	1.53** (1.31, 1.78)
Highest	3.40** (2.86, 4.04)	3.52** (2.99, 4.14)	1.39** (1.12, 1.73)	1.00 (0.76, 1.33)	0.08 (−0.05, 0.21)	1.49** (1.27, 1.75)
Child/newborn related factors						
Number of living children						
1	1	1	1	1	Ref	1
2–3	0.78** (0.70, 0.88)	0.63** (0.56, 0.70)	1.00 (0.85, 1.16)	1.00 (0.81, 1.23)	0.16** (0.07, 0.25)	1.00 (0.90, 1.12)
4+	0.51** (0.40, 0.64)	0.34** (0.28, 0.41)	0.73* (0.56, 0.95)	1.21 (0.87, 1.66)	0.39** (0.23, 0.54)	0.91 (0.76, 1.10)
History of child mortality						
No	1	1	1	1	Ref	1
Yes	1.30** (1.10, 1.53)	0.93 (0.80, 1.09)	0.97 (0.79, 1.20)	1.08 (0.84, 1.40)	0.01 (−0.11, 0.13)	0.84* (0.72, 0.98)
Sex of newborn						
Female	—	—	—	—	—	1
Male	—	—	—	—	—	1.20** (1.10, 1.31)
Health service-related factors						
Distance of nearest health facility with delivery care						
≤5 km	1.25** (1.14, 1.39)	1.12* (1.02, 1.23)	0.97 (0.79, 1.20)	1.08 (0.92, 1.40)	—	1.13** (1.03, 1.23)
5 + km	1	1	1	1		1
CHW's home visit during ANC						
No	1	1	1	1	Ref	1
Yes	2.89** (2.57, 3.25)	0.91 (0.81, 1.03)	1.04 (0.89, 1.22)	1.01 (0.83, 1.23)	−0.03 (−0.13, 0.07)	1.04 (0.93, 1.16)
Received neonatal danger sign counseling after delivery						
No	—	—	—	—	Ref	1
Yes	—	—	—	—	0.12* (0.02, 0.21)	1.12* (1.01, 1.25)

*p-value < 0.05.
**p-value < 0.01.
[£]AOR, adjusted odd ratio.
[¥]Aβ, adjusted beta coefficient of multiple linear regression.

quintile. Additionally, the wealth quintile indirectly mediated the neonatal care-seeking by increasing the odds of receiving ANC (AOR ranged: 1.30–3.40), facility delivery (AOR ranged: 1.45–3.52), and PNC (AOR ranged: 1.27–1.39). On the other hand, maternal education only indirectly increased the odds of neonatal care-seeking through increasing the knowledge of neonatal danger signs (Aβ ranged: 0.22–0.47), maternal PNC (AOR ranged: 1.68–2.22), facility delivery (AOR ranged: 1.39–1.88) and four or more ANC (AOR ranged: 1.36–2.62) in higher educated groups. Likewise, maternal age also was not associated with neonatal care-seeking behavior directly, however, it significantly increased

TABLE 3 Indirect effect, direct effect, total effect and mediating proportion of predictors on neonatal care-seeking (mediation analysis result).

Indicators	Indirect effect		Total indirect effect Log Odds (95% CI)	Direct effect Log Odds (95% CI)	Total effect Log Odds (95% CI)	Mediation proportion (%)
	Mediator	Indirect effect Log Odds (95% CI)				
Maternal health care utilization related factors						
4 + ANC from qualified providers	Facility delivery	0.24** (0.12, 0.39)	0.40** (0.27, 0.52)	0.23** (0.13, 0.34)	0.63** (0.49, 0.78)	63.5%
	PNC from qualified providers	0.06* (0.01, 0.12)				
	Knowledge on neonatal danger sign	0.09* (0.02, 0.16)				
Facility delivery	PNC from qualified providers	0.60* (0.12, 1.08)	0.47* (0.02, 0.98)	0.26** (0.13, 0.39)	0.74* (0.30, 1.17)	63.5%
	Knowledge on neonatal danger sign	−0.13* (−0.24, −0.02)				
PNC from qualified providers	Knowledge on neonatal danger sign	0.34* (0.07, 0.60)	0.34* (0.07, 0.60)	0.16* (0.03, 0.29)	0.50** (0.21, 0.78)	68.0%
Maternal background factors						
Mother's age	Facility delivery	0.12** (0.04, 0.19)	0.20** (0.09, 0.31)	–	0.20** (0.09, 0.31)	–
	Knowledge on neonatal danger sign	0.08* (0.002, 0.16)				
Mother's education	4 + ANC from qualified providers	0.14** (0.05, 0.23)	0.48** (0.32, 0.63)	–	0.48** (0.32, 0.63)	–
	Facility delivery	0.12** (0.04, 0.21)				
	PNC from qualified providers	0.10* (0.01, 0.18)				
	Knowledge on neonatal danger sign	0.12* (0.01, 0.22)				
Wealth quintile	4 + ANC from qualified providers	0.16** (0.08, 0.24)	0.49** (0.37, 0.61)	0.37** (0.25, 0.50)	0.86** (0.70, 1.02)	57.0%
	Facility delivery	0.21** (0.10, 0.32)				
	PNC from qualified providers	0.12* (0.02, 0.22)				
Child/newborn related factors						
History of child death	4 + ANC from qualified providers	0.06* (0.01, 0.10)	0.06* (0.01, 0.10)	−018.* (−0.33, −0.02)	−0.12 (−0.28, −0.04)	−50.0%
Number of living children	4 + ANC from qualified providers	−0.11** (−0.17, −0.05)	−0.26** (−0.40, −0.12)	–	−0.26** (−0.40, −0.12)	–
	Facility delivery	−0.21** (−0.31, −0.10)				
	PNC from qualified providers	−0.05 (−0.11, 0.01)				
	Knowledge of neonatal danger sign	0.10* (0.01, 0.19)				
Male sex of newborn	–	–	–	0.18** (0.10, 0.23)	0.18** (0.10, 0.23)	–

(*continued*)

TABLE 3 Continued

Indicators	Indirect effect		Total indirect effect Log Odds (95% CI)	Direct effect Log Odds (95% CI)	Total effect Log Odds (95% CI)	Mediation proportion (%)
	Mediator	Indirect effect Log Odds (95% CI)				
Health service-related factors						
Lower distance of nearest health facility	4 + ANC from qualified providers	0.05* (0.02, 0.09)	0.08** (0.04, 0.13)	0.12** (0.03, 0.21)	0.20** (0.10, 0.30)	40.0%
	Facility delivery	0.03* (0.002, 0.06)				
CHW's home visit during ANC	4 + ANC from qualified providers	0.24** (0.13, 0.36)	0.24** (0.13, 0.36)	–	0.24** (0.13, 0.36)	–
Received neonatal danger sign counseling after delivery	Knowledge of neonatal danger sign	0.08 (−0.01, 0.18)	0.08 (−0.01, 0.18)	0.11* (0.01, 0.22)	0.20* (0.06, 0.34)	40.0%
Neonatal danger sign knowledge						
Neonatal danger sign knowledge	–	–	–	0.37* (0.09, 0.64)	0.37* (0.09, 0.64)	–

*p-value < 0.05.
**p-value < 0.01.

the neonatal danger sign knowledge consistently (Aβ ranged: 0.22–0.47).

Among the child-related factors, neonatal care-seeking was higher for male children compared to female children (AOR: 1.20, 95% CI: 1.10, 1.31). This could be due to the higher percentage of male children who experienced severe danger signs (54.4%, $p = 0.001$) compared to female children (50.8%); and no difference was seen in qualified care-seeking ($p = 0.075$) during those severe danger signs (Supplementary Table S1). The odds of care-seeking were lower among mothers who had a history of child death (AOR: 0.84, 95% CI: 0.72, 0.97). Having more children significantly decreased the odds of ANC, facility delivery, and PNC, but increased the odds of knowledge of neonatal danger signs.

Among health service indicators, a shorter distance to the nearest health facility (≤5 km) not only directly increased the likelihood of neonatal care-seeking behavior (AOR: 1.13, 95% CI: 1.03, 1.23) but also indirectly increased the odds of neonatal care-seeking by increasing the odds of ANC (AOR: 1.25, 95% CI: 1.14, 1.39) and facility delivery (AOR: 1.12, 95% CI: 1.02, 1.23). Furthermore, receipt of counseling on neonatal danger signs not only directly increased the chance of neonatal care-seeking (AOR: 1.12, 95% CI: 1.01, 1.25) but also indirectly increased neonatal care-seeking by increasing knowledge of neonatal danger signs (Aβ: 0.12, 95% CI: 0.02, 0.21). Having received a CHW home visit during ANC did not impact care-seeking (AOR: 1.04, 95% CI: 0.93, 1.16), though it might have some positive indirect impact on care-seeking by increasing the odds a woman received ANC (AOR: 2.89, 95% CI: 2.57, 3.25).

Estimating the direct, indirect and total effect of predictor variables on newborn care-seeking

Table 3 shows the decomposition of direct, indirect, and summative total effect (in terms of Log Odds) of the significant inter-related predictors on neonatal care-seeking identified in the above GSEM model (Table 2).

Among the maternal health care indicators, ANC, facility delivery, and PNC had a direct effect on neonatal care-seeking [ANC::Log Odds (LOD): 0.23, 95% CI: 0.13, 0.34; Facility delivery::LOD: 0.26, 95% CI: 0.13, 0.39; PNC::LOD: 0.16, 95% CI: 0.03, 0.29]. Similarly, ANC, facility delivery and PNC also indirectly increased neonatal care-seeking [ANC::Log Odds (LOD): 0.23, 95% CI: 0.13, 0.34; Facility delivery::LOD: 0.26, 95% CI: 0.13, 0.39; PNC::LOD: 0.16, 95% CI: 0.03, 0.29]. The proportions of indirect effects of ANC, facility delivery and PNC were higher than the direct effect (Mediation proportion range: 63.5%–68.0%). ANC had 3 mediating pathways, and among those, facility delivery was the most proximate to the ANC and mediated the highest indirect effect (LOD: 0.24). Similarly, facility delivery had 2 mediating pathways and the highest indirect effect of facility delivery was mediated through PNC (LOD: 0.60). Finally, all of the indirect effects of PNC were mediated through the women's knowledge of neonatal danger signs (LOD: 0.34). Maternal health utilization factors (ANC, facility delivery, and PNC) had the highest summative total effects (Log Odds (LOD): 1.80) comparing the summative total effect of each maternal background, child/newborn, and health service-related factors.

Among the maternal background factors, household wealth had both direct (LOD: 0.37, 95% CI: 0.25, 0.50) and indirect effects (LOD: 0.49, 95% CI: 0.37, 0.61). This indirect effect was also the highest among all indirect effects and mediated through ANC, facility delivery, and PNC. Household wealth showed the highest total effect (LOD: 0.86, 95% CI: 0.70, 1.02) among all other predictors of neonatal care-seeking. On the other hand, maternal education did not show any direct effect, though it showed the second highest indirect effect among all other predictors of neonatal care-seeking (LOD: 0.48, 95% CI: 0.32, 0.63).

Among the child-related factors, the likelihood of neonatal care-seeking was higher among the male children (LOD: 0.18, 95% CI: 0.10, 0.23), while care-seeking was less among mothers who had a history of child death (LOD: −0.12, 95% CI: −0.28, −0.04). Similarly, neonatal care-seeking was lower among the mothers with more children (LOD: −0.26, 95% CI: −0.40, −0.12).

Among the health service-related indicators, receipt of a CHW visit during pregnancy indirectly increased neonatal care-seeking (LOD: 0.24, 95% CI: 0.13, 0.36). Following the CHW visit, distance to the nearest health facility and receiving counseling on neonatal danger signs after delivery each increased the total log odds of neonatal care-seeking by 0.20 times (95% CI: 0.10, 0.30 and 0.06, 0.34 respectively).

On the other hand, as the most proximal predictor, women's knowledge of neonatal danger signs only directly increased the log odds of neonatal care-seeking (LOD: 0.37, 95% CI: 0.09, 0.64). It was also the significant mediating channel for most other variables of the conceptual framework.

Discussion

This study found a high prevalence (one of every two neonates) of neonatal danger signs in the first month after birth, which was consistent with the findings of other studies conducted in Bangladesh (9, 26). Although almost all mothers of infants with danger signs sought care, only one-third sought care from a qualified health provider, which was consistent with a recent study in Bangladesh (23). Two-thirds of mothers sought care from untrained providers, which include village doctors, homeopathic practitioners, and local drug stores. In Bangladesh, village doctors are the most frequent choice due to easy access, and because their services are relatively cheap and culturally acceptable (21, 23, 26, 40, 41). In addition, parents believe that homeopathic medicine is mild and has a gentle effect, is easy to administer, and has no side effects, and thus, is considered more suitable for neonates (26, 42). Training of unqualified providers on timely referral to health facilities could be considered to facilitate the appropriate diagnosis and treatment of sick neonates (26).

Among the maternal health utilization factors, ANC, facility delivery, and PNC from qualified providers directly increased neonatal care-seeking from a qualified provider, which was similar to other studies (23, 24, 43, 44). Previous visits to qualified providers increase not only the trust, but also awareness about the availability of newborn care services, and the importance of care-seeking from trained health personnel during an illness episode (23, 26, 45). On the other hand, the indirect effects of ANC, facility delivery and PNC were larger than the direct effect. In conventional determinant analysis, only the direct effects are calculated, which underestimates the overall total effect of a predictor variable on the outcome variable. Therefore, in addition to the direct effect, the greater indirect effect implies the further importance of these factors as the determinants of neonatal care-seeking.

In summary, the highest summative effect of maternal health factors (ANC, facility delivery, and PNC) on newborn care-seeking over other factors domains suggests that ensuring mothers' use of services along the continuum from pregnancy through the postnatal period should be the key programmatic focus of maternal and child health care interventions. For improving the maternal care continuum, some integrated community and health facility-based interventions with the deployment of adequate community-based skilled providers with strong monitoring for continuity were found successful in Bangladesh (46, 47) and other countries (48–50). But further scaling up requires addressing some policy-level challenges, such as recognition of community-based intervention, increasing sustainability and retention of community health workers, addressing the shortage of human resources in public health care, ensuring health workers stay at primary level facilities and innovation in public-private partnership (46, 47, 51). For a resource-poor country like Bangladesh, mobile health (mHealth) strategies have shown promise to improve the timely maternal care continuum (52–54). The national health information management system (HMIS) could be leveraged by integrating a low-cost mHealth innovation within it. Studies also identified the quality of care of maternal health services as an important determinant of the utilization of an adequate number of ANC, facility delivery, and PNC from skilled providers (51, 55–57). Therefore, the quality of maternal care also needs to be prioritized as part of health system strengthening efforts.

Household economic status had the highest total effect on newborn care-seeking, with an almost equal amount of direct and indirect effects; and all indirect effects were mediated through ANC, facility delivery, and PNC. Household income is an enabling factor for care-seeking; and it is obvious that the treatment, medicine, transportation, and opportunity cost for care-seeking are key barriers for poorer households (58–60). In many settings including Bangladesh, demand-side financing (DSF) schemes, such as conditional cash transfers or vouchers; and expansion of services in low-coverage areas for the poorer households have been reported to be effective to reduce inequities for all socioeconomic groups in maternal and child healthcare utilization (61–64). On the other hand, maternal education did not show any direct effect on neonatal care-seeking, which was similar to other study findings (24, 26). However, maternal education did indirectly show a substantial effect on neonatal care-seeking through ANC, facility delivery, PNC, and the mother's knowledge of newborn danger signs. The total indirect effect size of maternal education was large enough to show that maternal education is an important positive factor for improving neonatal care-seeking.

Our study results showed higher care-seeking practices for male newborns compared to females. However, this higher likelihood of care-seeking was explained by the higher number of severe complications among the male neonates, but equal care-seeking proportion during those complications (**Supplementary Table S1**). Previous studies from Bangladesh have shown a significant sex differential in neonatal care-seeking (21, 24, 26, 65, 66); while our study suggests that there is no apparent gender bias in neonatal care-seeking.

Among the health service-related factors, distance to the nearest health facility was directly and indirectly associated with neonatal care-seeking from qualified providers, which is a similar finding to other studies conducted in Bangladesh (24, 67). Long distance to the nearest health facility is a major barrier to accessing health care services (68–71). The government's standard operating procedure for sick newborns requires referring to Upazila Health Complex (UHC) or District Hospital (DH) (72). At the sub-district level, there is only one UHC (73) and mothers may refuse referral for various reasons including distance to the referral facility, poor roads, or lack of transportation. However, sick newborns with suspected bacterial infections who can't be referred for any reason need to be treated with antibiotics at a primary (Union) level facility (74). The government should encourage and improve local providers' adherence to guidelines for antibiotic treatment for referral-refused mothers (74). Among other health service factors, counseling on neonatal danger signs after delivery, however, did demonstrate a positive effect in increasing woman's knowledge of neonatal danger signs and subsequently increasing the likelihood of care-seeking from qualified providers for newborn illness (24).

In our conceptual model, neonatal danger sign knowledge was the most proximal factor to neonatal care-seeking; having only a direct effect on care-seeking (75–78) and serving as a mediating channel for most factors to affect neonatal care-seeking for illness episodes. Our study results showed low knowledge levels among women about danger signs. The care-seeking from qualified providers was high if mothers perceived the danger signs as severe (49.0%). However, for actual medically identified severe neonatal danger signs (79–83), care-seeking was low (35.6%) (**Supplementary Table S2**), which implied the wrong judgment about the severity of danger signs (84). This evidence deems the importance of raising maternal awareness about newborn danger signs, most importantly, raising awareness regarding the severity and subsequent qualified care-seeking options. Counseling and health education should be strengthened at the available contact points during the antenatal, delivery, and postnatal periods at the facility and in the community (75, 78).

Strengths and limitations

To our knowledge this is the first study that assessed the direct, indirect, and total effect of predictor variables in explaining neonatal care-seeking for neonatal illness/danger signs through GSEM and mediation analysis, using a population-based survey with large sample size. However, our study has some limitations. The data used in our study was cross-sectional and therefore the analysis can't confirm the direction of causality between variables. Additionally, SEM/GSEM analysis is based on a hypothetical model with some simultaneous multivariable regression models. Perfect model identification for each simultaneous regression model may not possible due to variables' availability given the nature of the study and dataset, which may lead to omitted variable bias (37, 85).

Conclusions

Unqualified village practitioners are the first contacts for most of the mothers of sick neonates. Therefore, training the informal providers on the timely referral of sick neonates to health facilities is important. The inter-relationship and highest summative effect of ANC, facility delivery, and PNC on newborn care-seeking suggested that ensuring the maternal care continuum altogether should be the key programmatic focus of maternal and child health care interventions to improve sick newborn care-seeking. Targeted intervention for poorer households and increasing the community health worker's home visits are also required to improve neonatal care-seeking. The effectiveness of danger sign counseling and higher maternal knowledge deemed the importance of danger sign counseling by the health care providers at the available contact points during the antenatal, delivery, and postnatal period at the facility and in the community. In summary, integrated community and health facility-based strategy combined with the innovation of health system strengthening should be the foundation of maternal and newborn health care utilization and saving newborn lives.

Data availability statement

The datasets presented in this article are not readily available because Due to ethical restrictions related to protecting study participants' privacy and confidentiality, data access is restricted by the Ethical Review Committee of icddr,

b. According to the icddr,b data policy (http://www.icddrb.org/policies), interested parties may contact Ms. Armana Ahmed (aahmed@icddrb.org) with further inquiries related to data access. Requests to access the datasets should be directed to Ms. Armana Ahmed (aahmed@icddrb.org).

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee of Save the Children USA and Institutional Review Board (IRB) of International Centre for Diarrhoeal Disease Research, Bangladesh (Protocol number: PR#18099). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SB, BB, SZ, UM and SA: contributed to the design of the MaMoni MNCSP project. SP: supervised the data collection. RA and SB: conceptualized the data analysis and prepared concept version of the manuscript under the guidance of SA. RA did the data analysis, wrote the first draft and addressed the comments of co-authors. BB, NA, SH, JJ, LG, SP SZ, SR, MR, UM, SA: critically reviewed the manuscript. SB, SH, JJ, LG: edited the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.929157/full#supplementary-material.

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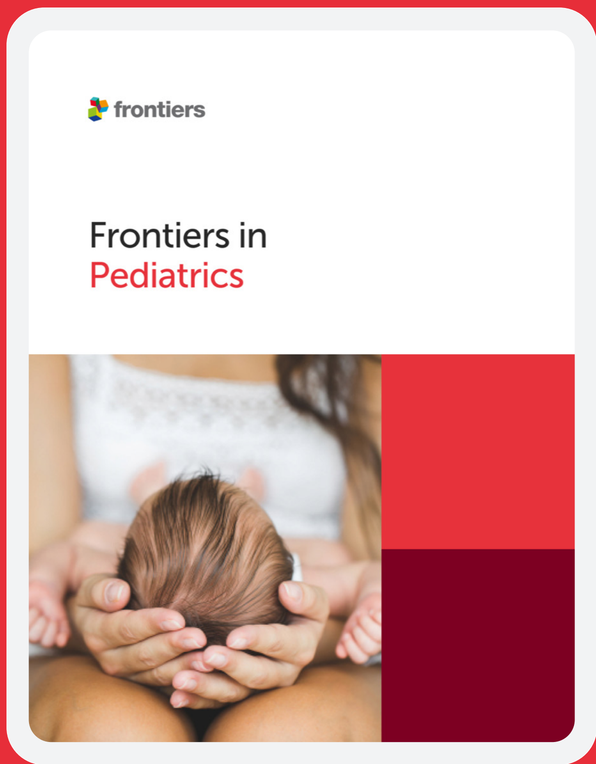

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