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EDITORIAL COMMENTARY

Hospital-onset Neonatal Sepsis and Mortality in Low-resource Settings: Will Bundles Save the Day?

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(See the Major article by Mwananyanda et al on pages 1360–7.)

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Over the last several years, rates of mortality in children <5 years of age in low- and middle-income countries (LMICs) have decreased, but reductions in neonatal mortality, or deaths occurring in the first 4 weeks of life, have proven more difficult to achieve [1, 2]. Among 2.5 million annual neonatal deaths, approximately one-third are due to infections, including sepsis and pneumonia [2]. Increasingly, a significant proportion of these deaths occur in the hospital setting, and many of these infection-related deaths may be preventable [3].

Many LMICs have implemented strategies to increase facility-based births in an effort to provide higher-quality care around the time of birth, especially for high-risk mothers [4, 5]. However, for mothers and vulnerable neonates, hospital-based care around the time of birth carries significant risks, including the risk of infection [5]. In many LMIC facilities, overcrowding and inadequate adherence to basic infection prevention and control (IPC) practices promote spread of antibiotic-resistant bacteria and contribute to hospital-onset infection and associated outbreaks [5]. Additionally, special care nurseries and neonatal intensive care units (NICUs) deliver advanced care that increases infectious risks associated with, for example, insertion and maintenance of central catheters and administration of medications and intravenous fluids [6].

In LMICs, identification and implementation of strategies to improve IPC practices and reduce risk of healthcare-associated infection (HAI) have not kept pace with the changing landscape of neonatal care in these settings. Efforts to reduce neonatal mortality due to infections in low-resource settings have focused largely on community-based interventions such as hand hygiene compliance among community health workers; use of sterile blades for cutting the umbilical cord; chlorhexidine cord care; and appropriate recognition, treatment, and potential referral of neonates with suspected sepsis to first-level healthcare facilities [4, 7]. While improvement of community-based services for mothers and neonates is critical to reduce neonatal deaths worldwide, the failure to adequately resource birthing facilities and improve infection prevention strategies neglects a significant opportunity to save neonates who succumb to infection.

In this issue of *Clinical Infectious Diseases*, Mwananyanda and colleagues describe the implementation of a 5-component IPC bundle and the associated reduction in hospital-onset bloodstream infection and mortality in Zambian neonates. This study highlights several key challenges of studying and implementing neonatal hospital-based IPC in low-resource settings, including the selection of single interventions vs bundled strategies, differences in the microbiology (and possibly reservoirs) of neonatal bloodstream infections, and the quality of data available to assess the impact of interventions.

Recognizing that there is not one single intervention that will eliminate risk of infection in hospitalized neonates, multiple interventions often are bundled as multimodal strategies to reduce HAI rates, such as seen with efforts to reduce central line–associated bloodstream infections in NICUs [8, 9]. Many studies testing IPC bundles use a quasi-experimental study design that measures the association of bundle implementation and HAI rates [10, 11]. Quasi-experimental studies provide weaker evidence to determine causality (whether the intervention itself led to the change), and this design does not offer the opportunity to measure the effect of individual bundle components [10]. However, in low-resource settings, multicenter randomized controlled trials to systematically assess the impact of a single IPC intervention may simply be infeasible and cost-prohibitive. Bundled interventions and pre- and postintervention measurement of infection rates and mortality provide important contributions to a body of evidence that can support practice changes to protect vulnerable neonates.

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Another challenge that is inherent to quasi-experimental studies and demonstrated in the current report is the impact of seasonal variation and the potential for unmeasured confounding. Why do hospital-onset bloodstream infection rates in this study increase during the dry season? Why would a bundled strategy reduce rates of infection in the dry season but have little apparent effect during the remainder of the year? These questions should not blunt enthusiasm in the overall reduction in mortality observed after implementation of this bundle; however, additional research is needed to understand questions raised by this study to inform future IPC bundles to reduce bloodstream infections and mortality in this setting. Following this cohort longer will allow the investigators to (1) assess sustained improvements in outcome and (2) perform additional analyses that account for correlation within the data structure and adjust for seasonal affects. Additionally, a longer follow-up period would avoid the use of multiple data sources to assess intervention impact on mortality and improve comparability of pre- and postintervention study periods.

Prior studies have demonstrated the feasibility of implementing inexpensive and locally available IPC interventions in low-resource settings. Gill and colleagues found that hand hygiene compliance improved and mortality decreased in 2 NICUs in the Philippines with the implementation of a simple IPC bundle, including alcohol-based hand rub at each bedside, staff education, and use of an infection control checklist, establishing the feasibility of IPC bundle implementation in a low-resource setting [11]. Both the Gill and Mwananyanda study teams carefully selected locally available, cost-effective bundle components that can ultimately be scaled up for use throughout other resource-limited settings.

It is also noteworthy that Mwananyanda and colleagues described an overwhelming predominance of a single causative organism of hospital-onset sepsis in their Zambian neonatal unit, with 70.1% of isolates identified as *Klebsiella pneumoniae*. The leading organisms of late-onset neonatal sepsis in the United States continue to be group B *Streptococcus* and *Escherichia coli*, though coagulase-negative staphylococci are most commonly identified in neonates admitted to the NICU [6, 12]. In many LMICs, there is an overwhelming predominance of gram-negative infections in hospitalized neonates, especially due to Enterobacteriaceae, which are frequently described in association with outbreaks in the NICU [3, 13]. To optimize strategies to improve hospital-based IPC practices in neonatal units in LMICs, future studies must explore the reservoirs of these organisms causing hospital-onset neonatal sepsis. Understanding these reservoirs of transmission will help inform selection of IPC bundle components to implement in LMICs.

We commend the authors for overcoming many challenges in their quest to reduce neonatal deaths due to hospital-onset infections. Critical readers should consider this study's limitations, but the resounding words that should echo from this study are "what is next" and "how can we do more" to help translate advances in IPC to low-resource settings where neonates are dying from preventable infections.

Notes

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