Time to tackle early-onset sepsis in low-income and middle-income countries

See **Articles** page e661

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In 2015, the UN adopted the Sustainable Development Goals (SDG) representing integrated actions to improve health, prosperity, and peace on the planet. SDG 3 focuses on health and specifically targets preventable neonatal deaths to achieve neonatal mortality below 12 per 1000 livebirths by 2030. Although, compared to 1990, neonatal mortality rates had been halved to 18 per 1000 livebirths by 2017, extrapolation of these trends indicate that we will fail to meet the SDG goals even in optimistic scenarios.[1] Neonatal infections account for over 3 million of the approximatively 20 million sepsis cases in children under 5 years,[2] with an average mortality of 7·6%.[3] Post-discharge mortality and long-term morbidities further aggravate this impact.[4] Altogether, these findings provide a strong impetus to identify and target potentially modifiable factors contributing to excess neonatal deaths due to sepsis worldwide.

In this context, results from the Burden of Antibiotics Resistance in Neonates from Developing Societies (BARNARDS) study presented in this issue of *The Lancet Global Health* provide valuable insights.[5] Contrary to previous studies limited to neonatal intensive care unit settings that miss pre-hospital deaths, the authors did a facility-based study and assessed 29 483 mothers with 30 557 livebirths across seven low-income and middle-income countries (LMIC) including those with high neonatal mortality in Africa and south Asia. Maternal socioeconomic, demographic, environmental, and health factors, as well as perinatal and facility-specific data, were prospectively captured and the birth cohort followed up longitudinally until 60 days, although in 55% of neonates, follow-up was available only up to a median of 7 days. The authors previously reported on microbiological and treatment characteristics of neonates with confirmed sepsis,[6] highlighting high rates of antimicrobial resistance, and questioning adequacy of current antibiotic treatment recommendations. In the present report, the authors focus on outcomes and risk factors in facility-born neonates, where one in six developed clinically suspected sepsis (166 per 1000 livebirths)—a quarter of which was microbiologically confirmed. All-cause mortality was seven times higher in infants with clinically suspected sepsis and 14 times higher in those with laboratory-confirmed sepsis compared with uninfected infants, confirming a major effect of sepsis on neonatal mortality. Incidence rates varied dramatically across sites; however, as the authors acknowledge, it remains difficult to untangle to what degree this represents true variability as opposed to methodological differences in laboratory techniques. Although the authors identify a range of risk factors such as caesarean section, preterm delivery, preterm rupture of membranes, and prenatal exposure to antibiotics, these often overlap and absence of information on chorioamnionitis as a key confounder make it challenging to draw firm conclusions on prioritising future interventions. In addition, it remains unclear whether perinatally acquired early-onset sepsis and hospital-acquired versus community-acquired late-onset sepsis can be reliably discriminated in the dataset, despite the fact that these entities could warrant fundamentally different approaches.[7] Finally, given strong associations of sepsis outcomes with quality of care, as well as with recognition, timing, and appropriateness of both maternal and infant treatment, future studies should assess such quality indicators.

Despite these limitations, the BARNARDS study illustrates the urgent need to develop and test effective interventions to prevent, diagnose, treat, and follow up neonatal sepsis in LMIC settings. First, 89% of suspected sepsis, and 66% of mortality in the study occurred within the first 7 days after birth. Yet some of the microbiological findings and risk factors contrast with early-onset sepsis cohorts from high-income settings. Great efforts in high-income countries on perinatal management, and on risk stratification of newborns coupled with low thresholds to treat, have allowed such countries to keep mortality from early-onset sepsis in term infants close to zero.[8] It is thus imperative to design appropriate and context-sensitive strategies against early-onset sepsis for resource-limited settings. Second, although the authors observed that maternal education was not associated with outcomes, this finding should not distract from the fact that maternal education remains an evidence-based strategy to reduce neonatal

mortality.[9] Third, parental awareness programmes to increase knowledge of signs of sepsis carry promise to fasten recognition of sepsis, but have not been studied extensively in LMICs. Finally, we know that sepsis is associated with long-term intellectual, behavioural, and psychological outcomes in very preterm neonates, children, and adults. Yet, to date, the long-term impact of early-onset sepsis in term or late preterm infants in LMIC largely remains unknown.

In summary, the BARNARDS study paves the way for concerted efforts to reduce the burden of neonatal sepsis worldwide. Such efforts are likely to be cost-effective given that neonatal sepsis causes over 8 million disability-adjusted life years in sub-Saharan Africa alone.[10] Future studies should seek to test strategies customised to LMIC settings to prevent, recognise, and treat the disease early.

We declare no competing interests.

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1 Hug L, Alexander M, You D, Alkema L. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. *Lancet Glob Health* 2019; **7:** e710–20.
2 Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; **395:** 200–11.
3 Fleischmann C, Reichert F, Cassini A, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. *Arch Dis Child* 2021; **106:** 745–52.
4 Nemetchek B, English L, Kissoon N, et al. Paediatric postdischarge mortality in developing countries: a systematic review. *BMJ open* 2018; **8:** e023445.
5 Milton R, Gillespie D, Dyer C, et al. Neonatal sepsis and mortality in low-income and middle-income countries from a facility-based birth cohort: an international multisite prospective observational study. *Lancet Glob Health* 2022; **10:** e661–72.
6 Thomson KM, Dyer C, Liu F, et al. Effects of antibiotic resistance, drug target attainment, bacterial pathogenicity and virulence, and antibiotic access and affordability on outcomes in neonatal sepsis: an international microbiology and drug evaluation prospective substudy (BARNARDS). *Lancet Infect Dis* 2021; **21:** 1677–88.
7 Giannoni E, Agyeman PKA, Stocker M, et al. Neonatal sepsis of early onset, and hospital-acquired and community-acquired late onset: a prospective population-based cohort study. *J Pediatr* 2018; **201:** 106–14.e4.
8 Achten NB, Klingenberg C, Benitz WE, et al. Association of use of the neonatal early-onset sepsis calculator with reduction in antibiotic therapy and safety: a systematic review and meta-analysis. *JAMA Pediatr* 2019; **173:** 1032–40.
9 Balaj M, York HW, Sripada K, et al. Parental education and inequalities in child mortality: a global systematic review and meta-analysis. *Lancet* 2021; **398:** 608–20.
10 Ranjeva SL, Warf BC, Schiff SJ. Economic burden of neonatal sepsis in sub-Saharan Africa. *BMJ Glob Health* 2018; **3:** e000347.