**Antibiotics for neonatal sepsis in low and middle income countries – where to from here?**

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**Key words**: antimicrobial therapy; antibiotic resistance; infection; neonate; sepsis

**Word count manuscript:** 698

*Author contributions:*

LJS wrote the initial draft, incorporated edits and takes responsibility for the entire content. EDC and AvR contributed to manuscript revision and approved the final version.

*Funding:*

Not applicable.

*Competing interests:*

None declared.

*Patient consent for publication:*

Not applicable.

**Commentary:**

# The 2017 Global Burden of Disease report published in *The Lancet* reported that sepsis results in 2·9 million deaths in children under age five [1], with the highest incidence and mortality rates observed in neonates [2; 3]. Neonatal sepsis leads to excess infant mortality even after discharge [4], and survivors may suffer from neurocognitive sequelae impacting later growth and development [5]. In striking contrast to the vast majority of neonatal trials which are performed in high income countries (HICs) such as Europe, Canada, Australia, and the United States, high quality large neonatal sepsis cohorts in low and middle income countries (LMICs), where sepsis disproportionally affects maternal and child health, have remained much less common [6]. This challenge is further potentiated by the rapid emergence of drug-resistant organisms globally, which increasingly jeopardize the effectiveness of the most effective therapy for sepsis since the discovery of penicillin by Alexander Fleming in 1928.

In Neonatal Intensive Care Units (NICUs), antimicrobial use is extremely common even in the absence of robust signs and laboratory markers of infection. In the recent no-more-antibiotics and resistance (NO-MAS-R) point prevalence study conducted across 84 NICUs from 29 countries, one in four neonates admitted to NICU was treated with antibiotics [7]. In the NeoPInS trial on procalcitonin-guided antimicrobial treatment for early-onset neonatal sepsis, less than one in fifty neonates treated with antibiotics had proven sepsis [8]. This scenario may not reflect the day-to-day reality in certain LMIC settings, where presentations during an advanced, sometimes moribund stage of infection occur more frequently. Several international initiatives have been launched to address the Global Action Plan on Antimicrobial Resistance by the World Health Organisation [9], such as the Global Antibiotic Research and Development Partnership (GARDP) whose mission is to *“to ensure that everyone who needs antibiotics receives effective and affordable treatment*.

In this context, the manuscript by Thomson *et al.* reporting on results from the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) study [10], led by an international consortium including sites in South East Asia and Africa, addresses a key knowledge gap of relevance for clinicians, researchers, and stakeholders in public health. The authors analysed 442 patients for whom whole genome sequencing data on isolates was available, out of 1,019 neonates recruited into the BARNARDS study with culture proven sepsis which had antibiotic data available. While the 2016 update by the WHO on empiric antibiotics for neonatal sepsis recommends the use of ampicillin plus gentamicin as first line therapy, in the BARNARDS study only 28.5% (n=111/390) of patients with Gram-negative isolates were found to be susceptible to this regimen. Other combinations such as ceftazidime-amikacin were found to have three-fold higher susceptibility rates and were associated with lower mortality (hazard ratio 0.316, 95%-CI 0.139 to 0.718) albeit the latter effect likely was confounded by country-specific factors. Of concern, susceptibility to ampicillin in Gram-negative and Staphylococcal infections was exceedingly rare, questioning the indication of ampicillin as a mainstay of neonatal sepsis treatment combinations. Furthermore, a resistance rate of 14.4% was observed for meropenem in Gram-negative isolates, which is worrying as meropenem may represent a last resort treatment option for resistant Klebsiella species, a common pathogen of early-onset neonatal sepsis in LMICs.

While this observational study has a number of limitations, such as high drop-out rate from follow-up possibly resulting in underestimation of mortality, lack of patient-level pharmacokinetic measures, country-specific bias, and high risk of confounding due to the lack of randomized treatment allocation, the integration of sequential clinical, genomic and microbiological, drug, and cost data across a large network in LMICs settings is exceptional, and will serve to inform urgently needed diagnostic and interventional trials in this field.

At present, increasing global antibiotic resistance is threatening progress against neonatal sepsis, prompting urgency to develop improved measures to effectively prevent and treat life-threatening infections in this high-risk group. To this end, the successful translation of the WHO resolution on sepsis will rely on the ability to deliver the right antibiotic to the right patient at the right time. The findings from the BARNARDS study call for randomized-controlled trials comparing mortality benefit and cost efficiency of different antibiotic combinations and management algorithms to safely reduce unnecessary antibiotic exposure for neonatal sepsis.

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