Neonatal sepsis: Challenges in data access, harmonisation and analysis to inform empirical antibiotic recommendations in South African neonatal units

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Severe bacterial and fungal infections (sepsis) are a leading cause of mortality among neonates in sub-Saharan Africa. In African neonatal units, most sepsis episodes are hospital acquired, and caused by Gram-negative, antimicrobial-resistant pathogens. With rising rates of antimicrobial resistance (AMR) in neonatal sepsis pathogens, there is an increasing probability of inappropriate empirical antibiotic therapy (so called 'bug-drug' mismatch or discordant therapy), as confirmation of pathogen identity and antibiotic susceptibility pattern is either not available or delayed. The impact of AMR and discordant empirical treatment on neonatal sepsis outcomes in Africa is largely unknown owing to the lack of the infection surveillance data needed to derive empirical antibiotic treatment recommendations. The Antibiotics for Neonatal Sepsis in Africa (ANSA) study will address this data gap by pooling and harmonising available single-centre research datasets and/or routine laboratory blood culture data to determine which antibiotics should be used for empirical treatment of neonatal sepsis. However, many challenges hamper these datasets, including: variable laboratory methods for pathogen identification and susceptibility testing; difficulty in collating and harmonising data from multiple sites; problems of record linkage in the absence of a single patient identifier; lack of centralised health data capturing systems; and difficulty accessing data due to complex data sharing agreements and custodian permissions. To overcome some of these challenges, minimum guidelines for the collection of neonatal sepsis data need to be defined, to ensure consistency between datasets. Greater collection of, access to and sharing of neonatal sepsis data from institutional, provincial and national laboratories, as well as individual neonatal units, would enable the establishment of a neonatal surveillance network. Development of a sustainably-funded neonatal sepsis surveillance network is a national priority, to ensure effective, evidence-based antimicrobial treatment of hospitalised neonates in South Africa.

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The first 28 days of life – the neonatal period – is the most vulnerable period for newborns. In 2020, sub-Saharan Africa (SSA) recorded the highest neonatal mortality rates in the world, with 27 deaths per 1 000 live births.[1] Although South Africa (SA) has already achieved the Sustainable Development Goal target of <12 deaths/1 000 live births,[2] >10 000 newborns died in 2020,[2,3] with 1 in 8 of these deaths attributed to severe bacterial/fungal infections or sepsis.[1,4] Infections in newborns are often life threatening owing to underdeveloped immune systems, with survivors experiencing lifelong neurodevelopmental sequelae.[5]

Treatment of neonatal sepsis includes the early administration of intravenous antibiotics with activity against the most prevalent bacterial/fungal pathogens. These treatment regimens by necessity are prescribed empirically (i.e. in the absence of immediate

laboratory confirmation, owing to the long turnaround time for microbiological cultures, or the lack of access to a diagnostic laboratory in many resource-limited settings).[6] The choice of empirical antibiotic regimens for neonatal sepsis is informed by factors such as the timing of infection onset, and the known susceptibility profile of pathogens in a specific neonatal unit.[7] Most antibiotic guidelines require regular updating, as pathogen distribution and antimicrobial resistance (AMR) rates change over time; however, this requires the availability of relevant datasets. For example, the World Health Organization (WHO)'s empiric antibiotic recommendations for neonatal sepsis have not been updated in several decades, largely owing to a lack of globally representative neonatal sepsis data.

The problem at hand

Rising AMR rates increase the likelihood of discordant or 'inappropriate' empirical antibiotic treatment of neonatal sepsis, which may exacerbate case fatality. Even when concordant antibiotic therapy is provided early, antimicrobial-resistant pathogens may be associated with higher mortality.[7] The true burden and impact of AMR in neonates from African countries are unknown, owing partly to a lack of microbiology laboratory services in many countries, but also owing to a failure to collect, harmonise and meaningfully analyse existing neonatal bloodstream infection (BSI) data. The overarching goal of the Antibiotics for Neonatal Sepsis in Africa (ANSA) study is to pool available single-centre research datasets and/or routine blood culture data from the National Health Laboratory Service (NHLS) serving public-sector facilities in SA to determine which antibiotics should be employed as empirical treatment for neonatal sepsis. However, in attempting to obtain, clean, harmonise and analyse these datasets, we have encountered several major challenges. This brief commentary aims to highlight these issues related to the use of available national operational and institutional health research datasets. We also propose possible avenues of improvement to enhance the use of neonatal sepsis data for health decision-making.

The study has research ethics approval from Stellenbosch University (ref. no. N20/07/070).

Data sources

The SA research datasets at the centre of the ANSA study are two-tiered: provincial and national. The regional dataset is based on confirmed neonatal sepsis (blood-culture positive with a known neonatal pathogen) at nine Western Cape Province healthcare facilities in 2017 and 2018. These facilities are classified based on their level of care (central, regional or district hospital), as well as whether neonatal surgery is undertaken onsite. A national dataset (a subset of the Baby GERMS-SA surveillance dataset) consists of all positive blood cultures obtained from babies ≤60 days of life hospitalised in neonatal units, including labour/postnatal wards, neonatal wards or neonatal intensive care units in public sector facilities across all nine SA provinces utilising the NHLS between 1 September 2019 and 31 August 2021. Babies hospitalised in paediatric wards or intensive care units were excluded. For both datasets, positive blood cultures were de-duplicated from isolate to 'episode' using identifier variables and excluding any repeat isolation of the same pathogen within 14 days of the original culture. Babies ≤60 days of age in the neonatal unit were included, as many extremely preterm neonates have prolonged hospital stays. A key difference between the regional and national neonatal sepsis datasets is that the former includes laboratory data (day of life at infection onset, pathogen, antibiotic susceptibility profile) and neonatal demographics (birthweight, gestation), length of hospital stay and outcome (alive/died), whereas the national neonatal sepsis data only include laboratory data and basic demographics (day of life at infection onset, sex).

Data challenges

In order to determine which empirical antibiotics would provide the greatest coverage for the variety of neonatal pathogens and different AMR patterns, infection episodes and AMR profile data must be available. However, the availability of organism details and resistance profiles varies between healthcare facilities. Should facility-specific data of BSI episodes be collected (similar to the regional dataset), clinicians would have control over the variables collected and could prospectively continue to collect data. However, small hospitals would have to collect several years of data in order to generate enough evidence for antibiotic recommendations. However, while collecting information from multiple sites would allow for more rapid generation of data, collating data from multiple sites can result in a lack of consistency in data entries and would be prone to capturing errors, especially for free-text variables, requiring a large number of resources expended on data preparation prior to its actual use. Particularly in the SA context, there is no central health data capturing system assigning a unique patient identifier. This poses a challenge in terms of record linkage both within the datasets, as well as across different datasets. Furthermore, obtaining access to available (especially multinational) data can often involve multiple data custodians and require complex data sharing agreements, regulatory or ethical approvals or permissions that could have extensive associated timelines and even discourage the usage of such data.

Recommendations

We advocate for a concerted effort to introduce a regional and national neonatal BSI surveillance network akin to the WHO Global Antimicrobial Resistance and Use Surveillance System (WHO GLASS).[8] To that end, we recommend that minimum guidelines for the collection of neonatal sepsis datasets be developed (Table 1). Variables of particular importance to guide antibiotic recommendations are day of life at sepsis onset, patient outcome (alive/died), empirical antibiotics administered at the time of blood culture specimen collection, pathogen identification and antibiotic susceptibility pattern, particularly for key antibiotics included in current empirical treatment guidelines, e.g. ampicillin, gentamicin, cefotaxime, piperacillin-tazobactam, amikacin and meropenem. This will bring about consistency when pooling datasets from multiple sites for national or regional antibiotic recommendations. In addition, we recommend a standardised reporting format to

Table 1. Recommendations for minimum data variables to support institutional, regional and national neonatal sepsis surveillance and antibiotic treatment guideline development

Laboratory variables (essential)	Hospital name
	Province name
	Ward name
	Age at blood culture (days)
	Organism name
	Antibiotic susceptibility profile
Demographic/clinical variables (ideal)	Sex
	Gestational age at birth
	Birthweight
	Date of admission
	Date of hospital outcome
	Patient outcome (alive/died)
	Empirical antibiotic(s) given for sepsis episode
Enablers of neonatal BSI surveillance and empirical antibiotic guidelines	Access for national bodies, key stakeholders and researchers to electronic neonatal sepsis datasets
	Harmonised data variables reported by laboratories and collected by institutions
	Annual collated, standardised reports of neonatal sepsis pathogen distribution and antimicrobial resistance rates
	Development of partnerships (regional, national, African) to advocate for, analyse and disseminate data on neonatal sepsis trends and antibiotic recommendations

BSI = bloodstream infection.

disseminate these essential laboratory data (at least annually) to national and provincial policy-makers to guide decisions on antibiotic recommendations, e.g. Essential Medicines List Committee, Department of Health and other key stakeholders such as the United South African Neonatal Association (USANA) and the Southern African Society for Paediatric Infectious Diseases (SASPID). Data access and sharing would require national and multinational regulatory bodies to work together to establish timeous and manageable agreements to ease the access and sharing of the neonatal sepsis data within and across borders. Stakeholder organisations, e.g. USANA, SASPID, the National Neonatal Sepsis Task Force and the African Neonatology Association, would be at the helm of forging better partnerships between local facilities nationally, and across Africa. Access to neonatal BSI surveillance data will enable updated and appropriate antimicrobial guidelines to ensure that clinicians prescribe antibiotics that are effective against the circulating neonatal sepsis pathogens.

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Conflicts of interest. None.

1. World Health Organization. Newborn mortality. Newsroom, 28 January 2022. https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-mortality-report-2021 (accessed 26 July 2022).
2. Sharrow D, Hug L, Lee S, Liu Y, You D. Levels and trends in child mortality, report 2021. New York: United Nations Children's Fund, 2021. https://www.who.int/publications/m/item/levels-and-trends-in-child-mortality-report-2021 (accessed 26 July 2022.)
3. Statistics South Africa. Recorded live births 2020. Pretoria: StatsSA, 2020. https://www.statssa.gov.za/?page_id=1854&PPN=P0305&SCH=73006 (accessed 26 July 2022).
4. Perin J, Mulick A, Yeung D, . Global, regional, and national causes of under-5 mortality in 2000-19: An updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health 2022;6(2):106-115. https://doi.org/10.1016/S2352-4642(21)00311-4
5. Global Antibiotic Research and Development Partnership (GARDP). Transforming the care of babies with sepsis. Geneva: GARDP Foundation, 2022. https://gardp.org/news-resources/gardp-neonatal-sepsis-study-report-2022/ (accessed 26 July 2022).
6. McGregor JC, Rich SE, Harris AD, . A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin Infect Dis 2007;45(3):329-337. https://doi.org/10.1086/519283
7. Cook A, Hsia Y, Russell N, . Association of empiric antibiotic regimen discordance with 30-day mortality in neonatal and pediatric bloodstream infection – a global retrospective cohort study. Pediatr Infect Dis J 2021;40(2):137-143. https://doi.org/10.1097/INF.0000000000002910
8. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report: Early implementation 2020. Geneva: WHO, 2020.

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