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A call to bridge the diagnostic gap: diagnostic solutions for neonatal sepsis in low- and middle-income countries

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INTRODUCTION

The first month of life is the most critical period for an infant's survival, yet the most neglected for the provision of quality care. Each year, an estimated 2.3 million neonates die in their first month of life.[1] Sepsis alone is responsible for 7.3% of all neonatal deaths worldwide, with a significant burden falling on low- and middle-income countries (LMICs).[2] While there remains an ongoing debate regarding the definition of neonatal sepsis, it is broadly described as a suite of non-specific signs that may include fever or hypothermia, respiratory distress, cyanosis and apnoea, feeding difficulties, lethargy or irritability, hypotonia, seizures, bulging fontanelle, poor perfusion, bleeding problems, abdominal distention, hepatomegaly, unexplained jaundice or more importantly 'just not looking right'.[3]

The absence of a conclusive, easily accessible and affordable diagnostic test for sepsis, as well as the multitude of potential pathogens, allows for ambiguity. This can result in underdiagnosis or overdiagnosis, both of which can have life-altering consequences for vulnerable neonates and their families.[4] Early intervention with antibiotics combined with triage and supportive care can be life-saving and can reduce the likelihood of long-term morbidity. Consequently, clinicians often find themselves compelled to trigger a sepsis protocol, which predominantly includes empiric antibiotics, even when the level of suspicion is low.[5 6] Overuse of antibiotics leads to the worsening of antimicrobial resistance (AMR), further undermining the effectiveness of antibiotics for neonatal sepsis, and minimises the importance of other elements of sepsis care.[7] In regions with scarce diagnostic resources, factors such as inadequate AMR surveillance data, antibiotic shortages and lack of up-to-date antimicrobial prescribing guidelines often necessitate that medical staff are left to administer antibiotics likely to be ineffective against local pathogens with high concomitant mortality and morbidity.[8] Furthermore, insufficient infection prevention and control measures

SUMMARY BOX

- ⇒ Low- and middle-income countries (LMICs) bear the greatest burden of neonatal mortality, with sepsis being a major contributor.
- ⇒ Non-specificity of signs, and the absence of a definitive diagnostic, present a challenge to the identification of sepsis and can lead to underdiagnosis or overdiagnosis, both of which can have harmful consequences.
- ⇒ As early intervention can be life-saving, sepsis protocols, which commonly include empiric therapies, result in the overuse of antibiotics and the development of antimicrobial resistance.
- ⇒ Affordable and accurate diagnostic tests that can detect neonatal sepsis at or near the point of care could contribute to reduced sepsis-related mortality in LMICs and support antimicrobial stewardship.
- ⇒ A screening test to guide referral to hospital from primary care, and an in-hospital test to guide treatment decisions, are high priorities.
- ⇒ Considerable investment will be needed to support the development of these diagnostics.

in neonatal intensive care units promotes the spread of microbes, allowing multidrug-resistant organisms to colonise hospital environments, further contributing to the AMR crisis and increasing the risk of neonatal infection.[9]

A recent literature review of care bundles for healthcare-associated infections in neonatal units in LMICs highlighted a significant gap in diagnosis: only 4% of bundle elements were related to detection.[10] Although blood culture is widely considered the gold standard for identifying bacterial and fungal infections, the high cost of testing versus the low cost of broad-spectrum antibiotic treatment and the sporadic availability of laboratories and personnel make it impractical for many facilities.[6] For neonates, this is exacerbated by challenges obtaining a blood sample of sufficient volume. Complex molecular diagnostic devices for pathogen detection, which have gained popularity in high-income countries, often face limitations when it comes to their applicability in LMICs, including their reliance on positive blood cultures, challenging environmental conditions and affordability constraints.

Host response diagnostics that use protein, metabolomic or transcriptomic biomarkers hold significantly more potential as pathogen-agnostic tools for diagnosing sepsis, but currently, there are no tests intended explicitly for neonates, and evidence supporting their use in LMICs remains scarce. Clinical algorithms and infection prediction scores may improve the accuracy of diagnosis as an adjunct to clinical judgement and reducing antibiotic use, but tend to have only moderate or low sensitivity and specificity, and few are validated in LMICs.[11]

BENEFITS AND CHALLENGES IN DEVELOPING NEONATAL SEPSIS DIAGNOSTICS

An affordable and accurate diagnostic test that can detect sepsis at or near the point of care could contribute to reduced infection-related mortality rates in LMICs, support the United Nations Sustainable Development Goal to reduce neonatal deaths to <12 per 1000 live births by 2030 and protect new and existing antibiotics through antimicrobial stewardship.

The distinctive characteristics of the neonatal immune system[12] lead to inherent individual variations that can affect the sensitivity of tests using host response markers over time.[13] One critical step towards developing a diagnostic for sepsis is defining specific use cases and attributes for the desired test. This can provide valuable guidance for product developers and other stakeholders on research priorities, facilitating the development of practical diagnostic tools.

USE CASES FOR NEONATAL SEPSIS TESTS

There are several clinical scenarios where a diagnostic tool would support a healthcare worker needing to decide whether to implement a sepsis protocol. UNICEF and NEST360 previously developed use cases for a potential point-of-care diagnostic for use in hospitals in LMICs based on a Delphi-like process.[14] In November 2022, FIND, NEST360 and UNICEF convened an expert group meeting to further discuss use cases and attributes of sepsis diagnostics. Priority tests were identified, including a screening test for use in primary healthcare and a test for in-hospital use (figure 1).

Screening test

A considerable proportion of neonatal sepsis deaths in LMICs occur outside hospital settings.[15] Due to its non-specific signs, neonatal sepsis can be very difficult for healthcare workers in primary care clinics to identify. Additionally, due to logistical challenges such as transportation costs and distance, referral from primary care to the hospital level is infrequent, even when neonatal sepsis is recognised. In conjunction with clinical training and support for healthcare workers, a neonatal sepsis test for use in primary healthcare facilities should increase the number of correct referrals, potentially saving lives and decrease unnecessary referrals, which would reduce the risk of acquiring healthcare-associated infections and lower the financial burden on healthcare systems and families. When referrals are not possible, the test could also inform antimicrobial and other treatment decisions.

In-hospital test

A diagnostic test for sepsis for use at the hospital level is the highest priority. While clinical judgement remains paramount, an objective test could provide valuable information to guide treatment decisions. By reducing the risk of missed cases and enabling clinicians to identify patients who do not require antibiotics, such a test could improve outcomes for neonates who do not require life-saving treatment while limiting the adverse effects of antibiotic overuse. It could also help healthcare workers determine whether a neonate should be admitted to a neonatal intensive care unit for advanced care, where the risk of acquiring a healthcare-associated infection and healthcare costs are usually higher.[10] In addition, it could serve as a triage tool to identify patients who would benefit from downstream microbiology testing, such as blood culture, pathogen identification and antibiotic sensitivity testing.

This diagnostic test would be of particular benefit for patients in a ‘diagnostic grey zone’, where it is unclear from clinical signs whether sepsis treatment is warranted. Success would rely heavily on the clinician’s perception of its accuracy. Hence, the diagnostic test should be accurate enough to ensure that the clinician can act confidently in accordance with the results. The diagnostic would need to be implemented together with appropriate training, clinical algorithms, patient monitoring and other alternatives to antibiotic treatment following a negative test result.

PATHOGEN-SPECIFIC AND AMR TESTS

Pathogen identification and antibiotic sensitivity tests would be valuable to inform the selection of appropriate

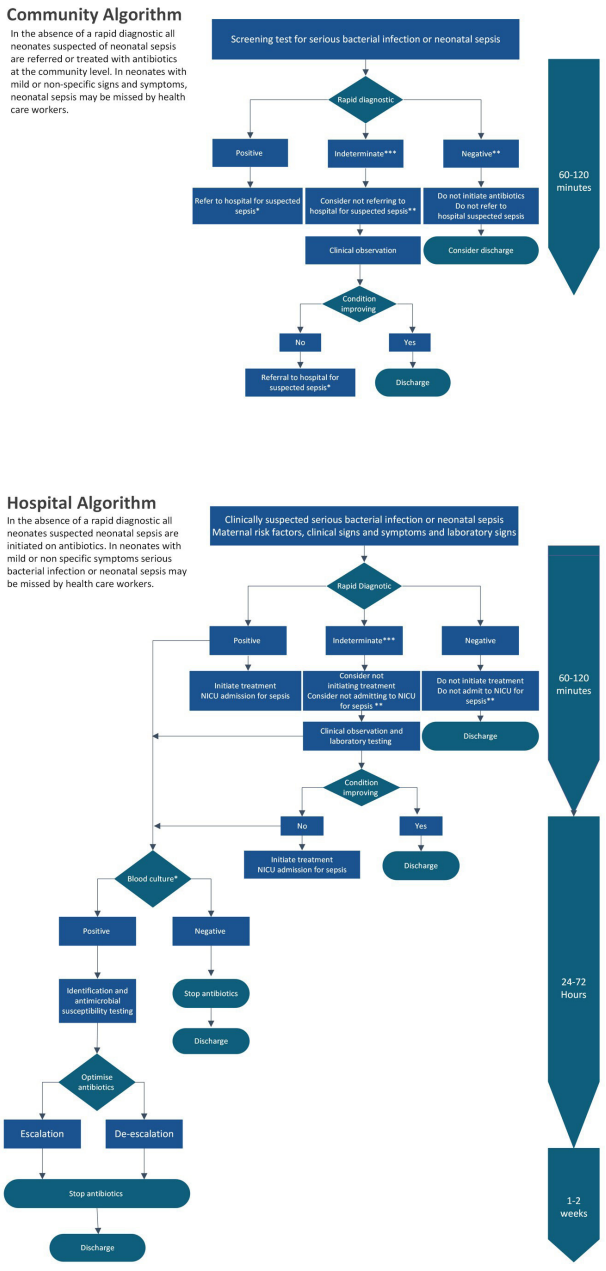

Figure 1 Algorithms for neonatal sepsis diagnostics in (A) community and (B) in-hospital settings. *Hospital referral - If hospital referral is not possible, treatment can be initiated according to local prescribing guidelines. **Neonates who have an indeterminate or negative test should still be evaluated, treated, monitored and referred for possible alternative diagnoses. ***Indeterminate: positive result from rapid diagnostic, but neonate appears well with no clinical signs and symptoms of a serious bacterial infection or sepsis or a negative result from rapid diagnostic, but neonate appears unwell with clinical signs and symptoms of a serious bacterial infection. *Blood culture - Perform if available. **Neonates who have an indeterminate or negative test should still be evaluated, treated, monitored, and referred for possible alternative diagnoses ***Indeterminate - Positive result from rapid diagnostic, but neonate appears well with no clinical signs and symptoms of a serious bacterial infection or sepsis or a negative result from rapid diagnostic, but neonate appears unwell with clinical signs and symptoms of a serious bacterial infection.

antibiotics. However, they are complex to develop and use and thus are likely to be restricted to hospital-level laboratories in LMICs. These tests would be less essential if reliable, up-to-date surveillance data were more widely available to guide clinicians on local resistance patterns for key pathogens and antibiotics. This level of surveillance is often not standard practice in LMICs due to the underutilisation or unavailability of blood culture and the need for better quality microbiology data.

FEASIBILITY OF DEVELOPING DIAGNOSTICS FOR NEONATAL SEPSIS

Several biomarkers have been evaluated as potential indicators of bacterial infection, including C reactive protein, procalcitonin and others.[13] These biomarkers cannot discriminate between infections caused by different pathogens, provide information on antibiotic susceptibility or provide insight into the level of organ dysfunction. Differences in study design, including the timing of testing, cut-off levels and definitions of overall, early and late sepsis, make biomarker studies challenging to compare, highlighting a need for a more concerted methodological approach. Some challenges could be addressed through serial testing or biomarker combinations. Existing or in-development platforms for host-response-based tests could be useful for the diagnosis of neonatal sepsis in LMICs but demonstration of sufficient performance in those populations and affordable pricing commitments are needed.

To suit LMICs, the diagnostic tests described above need to be robust and easy to use. Key attributes include accuracy, affordability, accessibility, rapidity, usability at or near the point of care, heat stability and low sample volume. Above all, the diagnostic test must have a demonstrable impact on clinical outcomes. To this effect, WHO, with the support of FIND, NEST360 and UNICEF, is planning to develop a target product profile to inform developers and researchers on the minimum and optimal attributes of tests that are well-adapted to the needs in LMIC settings.[16]

CONCLUSIONS

Diagnostics that help neonates get the right treatment at the right time would reduce mortality and morbidity and prevent the further escalation of AMR. However, these tests would not be standalone solutions and would need to be embedded into health systems that include hospital-based testing, monitoring and surveillance, infection prevention and control measures, community support and treatment and diagnostic stewardship. Considerable investment, innovation and collaboration will be needed to achieve the ambitious but realistic goal of developing effective diagnostics for neonatal sepsis.

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REFERENCES

1 United Nations Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality.2023, Available: https://childmortality.org/wp-content/uploads/2024/03/UNIGME2023-Child-Mortality-Report.pdf
2 UN Inter-agency Group for Child Mortality Estimation. *CME Info* 2023.
3 Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. *Virulence* 2014;5:170–8.
4 Molyneux E. Severe neonatal bacterial infections: when numbers matter. *Lancet Infect Dis* 2014;14:665–7.
5 Seale AC, Blencowe H, Manu AA, *et al*. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis. *Lancet Infect Dis* 2014;14:731–41.
6 Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. *J Trop Pediatr* 2015;61:1–13.
7 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.
8 Laxminarayan R, Matsoso P, Pant S, *et al*. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016;387:168–75.
9 Carvalho MJ, Sands K, Thomson K, *et al*. Antibiotic resistance genes in the gut microbiota of mothers and linked neonates with or without sepsis from low- and middle-income countries. *Nat Microbiol* 2022;7:1337–47.
10 Molina García A, Cross JH, Fitchett EJA, *et al*. Infection prevention and care bundles addressing health care-associated infections in neonatal care in low-middle income countries: a scoping review. *EClinMed* 2022;44:101259.
11 Lloyd LG, Dramowski A, Bekker A, *et al*. Performance Comparison of Infection Prediction Scores in a South African Neonatal Unit: A Retrospective Case-Control Study. *Front Pediatr* 2022;10.
12 Wynn JL, Levy O. Role of innate host defenses in susceptibility to early-onset neonatal sepsis. *Clin Perinatol* 2010;37:307–37.
13 Celik IH, Hanna M, Canpolat FE, *et al*. Diagnosis of neonatal sepsis: the past, present and future. *Pediatr Res* 2022;91:337–50.
14 UNICEF, NEST360. Use cases: sepsis diagnostic - infection prevention and control. 2020. Available: https://www.unicef.org/supply/media/2946/file/sepsis-diagnostic-use-cases.pdf [Accessed 15 Feb 2023].
15 Mahtab S, Madewell ZJ, Madhi SA, *et al*. Stillbirths and 0-90 days death caused by group b streptococcus in africa and south asia identified through child health and mortality prevention surveillance (CHAMPS). 4th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); Lisbon, 2023
16 Call for public consultation: target product profile for tests of neonatal sepsis and possible serious bacterial infections in newborns and young infants (who.int), Available: https://www.who.int/news-room/articles-detail/call-for-public-consultation-target-product-profile-for-tests-of-neonatal-sepsis