

New research on preventing infant deaths due to neonatal sepsis

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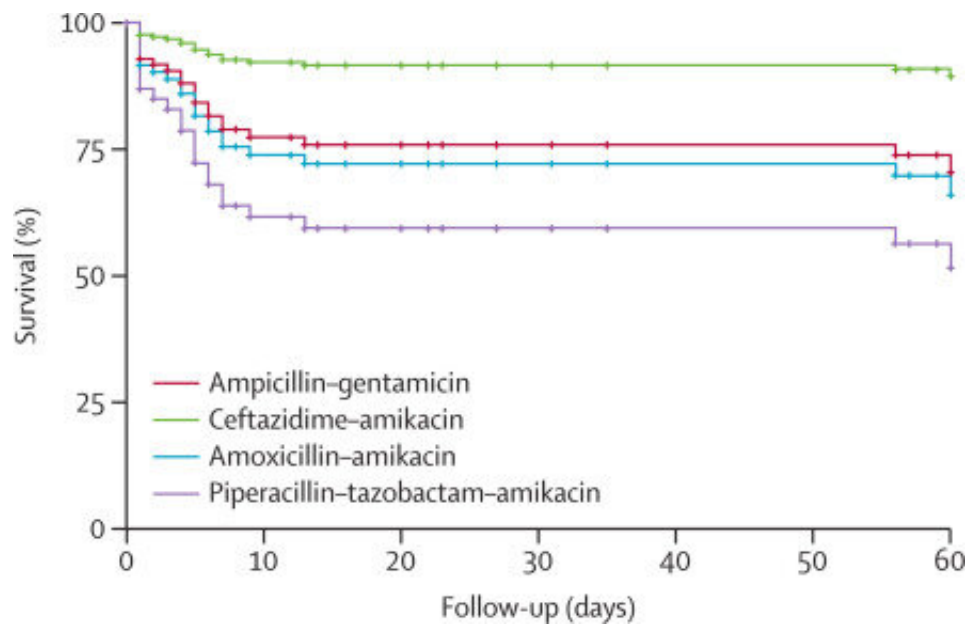


Figure 2. Survival analysis for neonates treated with each antibiotic therapy. Analysis was done for 476 neonates through Cox regression hazard ratios, adjusted for clinical factors. Clinical variables considered included cohort, sex, type of pathogen (ie, Gram-negative vs Gram-positive); whether the neonate was delivered via cesarean section; and whether the neonate was premature (appendix, pp 14–15) and stratified for onset of sepsis (early-onset sepsis or late-onset sepsis) to meet proportional hazard assumptions. For the purpose of this survival curve, the following clinical variables were set: male sex, inborn cohort, early-onset sepsis, Gram-negative sepsis pathogen type, no cesarean section, and no premature neonates. Credit: DOI: 10.1016/S1473-3099(21)00050-5

Information about the most effective antibiotics to use in low and middle-income countries (LMICs) for neonatal sepsis has been discovered uniquely combining epidemiological, genomic and pharmacodynamic data. The research could be applied to potentially save many lives globally by increasing the effective treatment—currently neonatal sepsis causes an estimated 2.5 million infant deaths annually. This research also highlights economic issues, specifically regarding treatment costs and other barriers to treatment.

The research published today in *The Lancet Infectious Diseases*, combined microbiology, genomic, epidemiological, pharmacodynamic and [economic data](#) for the first time to study the efficacy of various antibiotic treatments for [neonatal sepsis](#) in seven low and [middle-income countries](#) (LMICs) across Africa and South Asia. This research was done by an international network led by the microbiologists at the Division of Infection and Immunity, Cardiff, in collaboration with researchers at the University of Oxford, the paper proposes alternative antibiotics for septic neonates which could drastically decrease new-born mortality.

This research, funded by the Bill and Melinda Gates Foundation, studied over 36,000 infants over seven countries, making it the largest study of its kind. Data was procured by Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS), a project run by Professor Tim Walsh, which collected data across seven countries between April 2015 and March 2018. Prof. Walsh joined the University of Oxford in 2021 to help established the Ineos Oxford Institute of Antimicrobial Research. BARNARDS collected data from Nigeria, Pakistan, Bangladesh, Rwanda, South Africa, Ethiopia, and India, allowing researchers to have a vast amount of data to analyze.

Neonatal [sepsis](#) causes an estimated 2.5 million infant deaths annually, with LMICs in sub-Saharan Africa and Asia having the highest mortality rates. These countries often have reduced access to resources such as

laboratory facilities to assess what sepsis-causing pathogens are present, and to discover more about associated antimicrobial resistance.

The World Health Organisation recommends the use of ampicillin and gentamicin for the empirical treatment of neonatal sepsis. Whilst these may be effective in higher income countries (HICs), there has long been speculation that they were less effective in LMICs due to different levels of antibiotic resistance and variation in common pathogens.

Researchers discovered that some sites are already using different antibiotics to those endorsed by the WHO, due to high resistance against these antibiotics. Those prescribed the recommended combination of ampicillin and gentamicin had a survival rate of 75% over 60 days. Conversely, where those prescribed ceftazidime and amikacin had a survival rate of over 90% over the same time period.

These findings will lead to additional follow-up studies; not least, intervention studies related to treatment and ensure that sepsis is treated with appropriate antibiotics and infection prevention and control practices.

The study also investigated the frequency of resistance to various antibiotics, which shows how frequently resistance may arise in susceptible bacteria against different antibiotics. Whilst varied antibiotics have been suggested for neonatal sepsis, this is the first study that has incorporated frequency of resistance data, allowing insight into how quickly a certain antibiotic could become redundant following extensive use, if selected as an alternative, allowing for more accurate recommendations on which antibiotics to be used.

Lead author Kathryn Thomson says, "Extremely high resistance (>97%) was found against ampicillin in Gram-negative sepsis causing isolates analyzed from BARNARDS sites. Furthermore, only 28.5% of Gram-

negative isolates were susceptible to at least one of the combined antibiotic therapy of ampicillin and gentamicin. While this may be a suitable empirical treatment for neonatal sepsis in high income countries, this data showcases that it is not an effective option for LMICs, who have different common pathogens and vastly increased resistance against these antibiotics. Many LMIC sites depend on recommended therapies, due to a lack of microbiology facilities to detect common species or resistance profiles. Therefore, further work is urgently needed to improve the sparsity of data in LMICs regarding prevalence and AMR in neonatal sepsis, a major contributor to neonatal mortality and to determine more effective alternative empirical treatments, taking affordability into account."

The other factor investigated in this study is economic impact on antibiotic use. The study examined the average earnings of people in LMICs. This was used to contextualize the impact of antibiotic costs on the average person, by comparing average wages with the vast discrepancies in costs of certain antibiotics in different countries. For example, piperacillin-tazobactam costs \$2.60 per day in India, which is a massive 76% of the average daily wage. By contrast, it costs \$20 a day in Nigeria, representing between 219% and 741% of the average daily wage depending on the area of the country.

The economic data raises questions about who should be responsible for costs of antibiotic treatment, given that more effective alternative antibiotic treatments are often inaccessible in LMICs due to lack of universal healthcare. When asked, six of the seven countries studied stated that the cost of antibiotics influenced which are prescribed. This is shown by the continued wide use of ampicillin and gentamicin, as they are consistently the most affordable antibiotics, despite being considered less effective than other antibiotic regimes for some time now.

Professor Tim Walsh says, "Whilst this study uniquely combined sets of

data to help address critical issues around the treatment of neonatal sepsis in LMICs, this study also highlighted gaps and the need for further critical data; not least, how the accessibility and cost of antibiotics impacts on therapeutic treatments and outcomes. The newly established IOI is committed to undertake such studies and establish new and dynamic international networks to provide the rigor of data that will hopefully further our understanding and address one of the most pressing issues in a critical patient population across LMICs."

Follow-up studies will be undertaken by the newly formed Ineos Oxford Institute at the University of Oxford, which will focus on new drug development for both human health and replacement of clinically relevant antibiotic use in agriculture, in addition to studying antibiotic resistance and ways of promoting more responsible and effective uses of [antibiotics](#).

More information: Luregn J Schlapbach et al, Antibiotics for neonatal sepsis in low-income and middle-income countries—where to go from here?, *The Lancet Infectious Diseases* (2021). [DOI: 10.1016/S1473-3099\(21\)00199-7](#)

Kathryn M Thomson 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), *The Lancet Infectious Diseases* (2021). [DOI: 10.1016/S1473-3099\(21\)00050-5](#)

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