Tackling antimicrobial resistance in neonatal sepsis

The reduction of maternal and child mortality, which has halved worldwide in the past two decades, is considered one of the greatest successes of the Millennium Development Goals programme.[1] However, the number of neonatal deaths has remained unacceptably high, with an estimated 2·9 million deaths every year (44% of all deaths in children younger than 5 years, worldwide).[2] In 2012, the most common causes of neonatal death globally were preterm-birth complications, intrapartum-related conditions, and infections.

Globally, infections cause nearly a quarter (23%) of all neonatal deaths, with neonatal sepsis accounting for 15% of these deaths.[1] Severe bacterial infections in neonates account for about 3% of all disability-adjusted life-years.[3] Prompt diagnosis and appropriate treatment are crucially important in reducing mortality. However, the worldwide spread of antimicrobial resistance represents a major challenge, with nearly half of the pathogens that cause severe neonatal bacterial infections reported to be resistant to the first-line (ampicillin or penicillin, and gentamicin) and second-line (third-generation cephalosporins) WHO-recommended treatments.[4] In 2016, the first estimate of neonatal deaths attributable

Panel: **Treatments expected to be developed as part of the NeoAMR Project**

Regimen 1

Indication
Empirical treatment of neonatal sepsis, including meningitis, in premature and term infants, early and late onset infection

Patient population
Neonates with possible severe bacterial infections in settings with a high prevalence of resistance to first-line WHO recommended treatment

Route of administration
Intravenous, 30 min infusions

Dosing schedule
Once or twice daily

Efficacy
Comparable to amoxicillin-gentamicin or ceftriaxone-gentamicin in claimed indication, with activity against pathogens that are resistant to amoxicillin-gentamicin or ceftriaxone-gentamicin

Treatment duration
5–10 days

Safety and tolerability
Low propensity for resistance development, large therapeutic window, minimal hepatotoxicity, nephrotoxicity, and central nervous system toxicity, no prolongation of the QT interval

Drug interactions
Similar to the first-line WHO empirical treatments

Key countries
South America, Asia, and Africa

Pharmacoeconomics
Reduction of intensive care unit and length of hospital stay (modelling)

Current standard of care
Amoxicillin-gentamicin or ceftriaxone-gentamicin, as per WHO recommendations

Regimen 2

Indication
Neonatal sepsis and meningitis, when multidrug-resistance—specifically carbapenem-resistant, Gram-negative pathogens—has been shown, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, or *Acinetobacter* spp

Patient population
Neonates admitted to hospital with severe infections, failure on optimal current treatment, and positive microbiological culture

Route of administration
Intravenous, 30 min infusion

Dosing schedule
Once or twice daily

Efficacy
Similar to existing options in claimed indication and activity in pathogens resistant to carbapenems

Treatment duration
5–10 days

Safety and tolerability
Low propensity for resistance development, large therapeutic window, minimal hepatotoxicity, nephrotoxicity, and central nervous system toxicity, no prolongation of the QT interval

Drug interactions
Similar to standard of care

Key countries
South America, Asia, and Africa

Pharmacoeconomics
Reduction of intensive care unit and length of hospital stay (modelling)

Current standard of care
Colistin monotherapy

to antimicrobial resistance was published,[5] with multidrug-resistant pathogens approximated to account for 30% of all global neonatal sepsis mortality.[5] Multidrug-resistant pathogens are a challenge in high-income countries, but are even more so in low-income and middle-income countries because of insufficient access to antibiotics, higher burden of infectious diseases, weak health-care systems, and resources limitations. Nowadays, multidrug-resistance Gram-negative bacteria are of the greatest concern in neonates because few therapeutic options are available.[6] Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE) are responsible for an increasing number of outbreaks of health-care-associated infection in neonatal intensive care units (NICUs), and are associated with substantial morbidity and mortality. The emergence and spread of ESBL and CRE among NICUs has inevitably led to the reintroduction of old antibiotics, such as colistin and fosfomycin, often with minimal information distributed on drug safety and optimal dosing.

Few data are available to support an optimal treatment of multidrug-resistant infections, even in adults, with very few randomised trials and most data coming from retrospective observational studies. Data[6,7] on the number of robust clinical studies assessing old or new antibiotics involving neonates indicate that a very small number of trials are being conducted—ie, globally less than ten antibiotic trials involving preterm infants have been conducted. To address this need for additional data, the Global Antibiotic Research and Development Partnership (GARDP), a joint initiative of WHO and the Drugs for Neglected Diseases initiative (DNDi) in support of the Global Action Plan for Antimicrobial Resistance, established a new priority-setting framework, with the mission to develop new antibiotic regimens to address drug-resistant infections, promote their responsible use, and make them accessible for all populations in need.[8] As part of this initiative, the GARDP has launched a neonatal sepsis programme, which will include the NeoAMR Project (to be launched on Nov 8, 2017). This project will aim to develop new, globally applicable, empirical antibiotic regimens and strategies for the treatment of neonatal sepsis that can be adapted to settings with varying prevalence of multidrug-resistant pathogens.

The specific aim of the NeoAMR Project is to develop two treatments targeting two specific areas of need. First, an empirical regimen that serves as an alternative to amoxicillin and gentamicin in areas where a high prevalence of ESBL Gram-negative bacteria pathogens are suspected, and second, a treatment regimen to be used in situations when carbapenem-resistant Gram-negative bacteria have been shown. The panel summarises the main characteristics expected of these treatments.

The lead candidate for the first regimen consists of a combination of fosfomycin and amikacin since this combination would ensure adequate central nervous system penetration (which is essential considering the high incidence of meningitis in neonates with sepsis), low resistance development, good safety profile, and broad spectrum of activity. For the second regimen, a hollow fibre infection model has been developed[9] to identify suitable candidate combinations. These regimens could consist of an optimally dosed polymyxin-based combination, or other antibiotics that are in development or recently registered for use in adults that could prevent the emergence of drug resistance while resulting in maximal antibacterial activity, or a combination of these drugs.

The global shortage of antibiotics that are available for use in neonates is of increasing concern, particularly given the increase of antimicrobial resistance and the marked paucity of research in this vulnerable population. Neonates should be more highly prioritised in research and development globally, including in the development of enhanced diagnostics that are practical for use in low-income and middle-income countries, combined with the provision of novel evidence-based treatment options that can be available worldwide. The NeoAMR Project will provide the general framework for the design and implementation of large-scale neonatal sepsis trials across different geographical settings. It will also become the platform for future initiatives in this area, including monitoring the ongoing effect of these initiatives, and will seek to ensure that its outcomes are translated into appropriate policies and guidelines at both national and global levels.

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1 Lawn JE, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. *Lancet* 2014; **384:** 189–205.
2 Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015; **385:** 430–40.
3 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.
4 Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics—systematic review and meta-analysis. *Arch Dis Child* 2013; **98:** 146–54.
5 Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016; **387:** 168–75.
6 Folgori L, Bielicki J, Heath PT, Sharland M. Antimicrobial-resistant Gram-negative infections in neonates: burden of disease and challenges in treatment. *Curr Opin Infect Dis* 2017; **30:** 281–88.
7 Folgori L, Bielicki J, Ruiz B, et al. Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review. *Lancet Infect Dis* 2016; **16:** e178–89.
8 Drugs for Neglected Diseases initiative. Global antibiotic research & development partnership (GARDP). 2016. https://www.dndi.org/diseases-projects/gardp/ (accessed July 11, 2017).
9 Ramos-Martín V, Johnson A, Livermore J, et al. Pharmacodynamics of vancomycin for CoNS infection: experimental basis for optimal use of vancomycin in neonates. *J Antimicrob Chemother* 2016; **71:** 992–1002.