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. 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). 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. Severe bacterial infections in neonates account for about 3% of all disability-adjusted life-years. 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.

In 2016, the first estimate of neonatal deaths attributable to neonatal sepsis was made. The Panel identified two regimens that could be developed as part of the NeoAMR Project.

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

<table>
<thead>
<tr>
<th>Regimen 1</th>
<th>Regimen 2</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Neonatal sepsis and meningitis, when multidrug-resistance—specifically carbapenem-resistant, Gram-negative pathogens—has been shown, including <em>Klebsiella pneumoniae</em>, <em>Pseudomonas aeruginosa</em>, or <em>Acinetobacter</em> spp</td>
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<tr>
<td><strong>Patient population</strong></td>
<td>Neutonates admitted to hospital with severe infections, failure on optimal current treatment, and positive microbiological culture</td>
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<tr>
<td><strong>Route of administration</strong></td>
<td>Intravenous, 30 min infusion</td>
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<td><strong>Dosing schedule</strong></td>
<td>Once or twice daily</td>
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<td><strong>Efficacy</strong></td>
<td>Similar to existing options in claimed indication and activity in pathogens resistant to carbapenems</td>
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<td><strong>Treatment duration</strong></td>
<td>5–10 days</td>
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<td><strong>Safety and tolerability</strong></td>
<td>Low propensity for resistance development, large therapeutic window, minimal hepatotoxicity, nephrotoxicity, and central nervous system toxicity, no prolongation of the QT interval</td>
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<td><strong>Drug interactions</strong></td>
<td>Similar to standard of care</td>
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<td><strong>Key countries</strong></td>
<td>South America, Asia, and Africa</td>
</tr>
<tr>
<td><strong>Pharmacoeconomics</strong></td>
<td>Reduction of intensive care unit and length of hospital stay (modelling)</td>
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<tr>
<td><strong>Current standard of care</strong></td>
<td>Colistin monotherapy</td>
</tr>
</tbody>
</table>
to antimicrobial resistance was published, with multidrug-resistant pathogens approximated to account for 30% of all global neonatal sepsis mortality. 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. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE) are responsible for an increasing number of outbreaks of healthcare-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 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. 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 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.


