

Hard to study, hard to treat: putting children at the centre of antibiotic research and development

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Newborn babies, infants, and children are substantially affected by antimicrobial resistance. Globally, infectious diseases remain a major cause of morbidity and mortality in children,¹ and an estimated 214 000 newborn babies died from drug-resistant bacterial infections in 2015.²

In addition, guidelines and evidence-based treatments are scarce to help manage the full range of life-threatening paediatric infections, and paediatric specialists often resort to prescribing off-label and unlicensed drugs on the basis of clinical experience.³ For example, ampicillin/benzylpenicillin with gentamicin have remained the treatment regimen recommended by WHO for neonatal and paediatric sepsis for 50 years, despite very high rates of reported resistance to aminopenicillins and aminoglycosides,⁴⁻⁶ because no new studies have been done that would result in updated guidelines.

Although regulatory agencies require companies to develop paediatric plans to evaluate new antibiotics, few drug development projects are dedicated to new antibiotics for newborn babies, infants, and children.⁷ In part, this reflects the challenges of doing trials in such a susceptible population.⁸ Importantly, steps are now being taken by drug regulators to provide guidance on the paediatric-specific requirements for the evaluation of medical products to treat bacterial infections, but this guidance alone will not be enough to address clinical needs globally.

Three key responses are required to address the absence of evidence-based paediatric antibiotic treatments. First, an appropriately resourced initiative is needed to accelerate the completion of paediatric clinical studies of newly registered antibiotics or drugs in the late stages of development. Clinical trials must be designed with due consideration of the challenges of recruiting newborn babies, infants, and children, pragmatically accepting that, for well-established classes of antibiotics, both efficacy and safety can be extrapolated from adult data.⁹ Pharmaceutical companies should be actively encouraged to recruit to trials in both low-burden and high-burden antimicrobial resistance settings, similar to the regulatory studies for new paediatric antiretrovirals. Older antibiotics that do not have appropriate paediatric indications, formulations, or dosing schedules should also be identified for further development.

Second, for both old and new drugs, additional strategic clinical trials are needed targeting key population groups and public health needs, so evidence-based guidelines can be developed for their appropriate use, including use in combination with, or co-administered with other drugs. Importantly, these are not necessarily the trials required for drug registration.

Third, to ensure all these recommendations can be applied in ways that take account of sub-populations, geographies, and diverse resistance patterns, an international antibiotic clinical trial network should be developed for newborn babies, infants, and children. This network should include high-income, medium-income, and low-income countries, focusing on antimicrobial resistance as a global problem. Such a network could design and conduct clinical trials that are acceptable to regulatory authorities but also answer the strategic questions for empirical therapy required by international guideline development bodies, such as WHO. A strong regulatory component of the network could focus on facilitating the development of master protocols and streamlined paediatric investigational plans, building on new initiatives such as the Conect4Children network, supported by the Innovative Medicines Initiative 2. This new network should work with existing and emerging paediatric infection trial groups and global funders to launch projects that focus on key antibiotics

that have been identified through the WHO's 2017 categorisation of antibiotics,¹⁰ with the support of the WHO Department of Maternal, Newborn, Child and Adolescent Health, and the WHO Essential Medicines Programme.

With an urgent need for action, the Global Antibiotic Research and Development Partnership (GARDP, a joint venture of WHO and the Drugs for Neglected Diseases *Initiative*), is working with partners to launch a Global Paediatric Antibiotic Platform addressing the three previously described concerns (Panel). Its aim is to deliver an optimised paediatric antibiotic treatment by 2023, with up to two additional projects in development. Landscape review of potential priority drug candidates is underway, and GARDP invites the pharmaceutical sector to work in partnership to develop paediatric indications for its drugs. GARDP is already implementing a programme to address sepsis in neonates.

Panel: Aims and interventions of the Global Antibiotic Research and Development Partnership Paediatric Antibiotic Programme

- Accelerate the paediatric development of key new antibiotics emerging from the drug pipeline and obtain a paediatric indication or recommendation for important older antibiotics
- Support the update of paediatric guidelines with evidence, taking into account an evolving epidemiology globally
- Build on existing paediatric clinical trial networks to key activities including regulatory and implementation studies

Newborn babies, infants, and children—an important and susceptible population that is hard to study and hard to treat— should be given the priority and attention they deserve, with increased attention and resources to promote research and development to tackle antimicrobial resistance.

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