

Phoebe CM Williams et al.

Expedited paediatric drug development

This online first version has been peer-reviewed, accepted and edited,
but not formatted and finalized with corrections from authors and proofreaders

Expedited research and approval of medicines for drug-resistant bacterial infections in children

Phoebe CM Williams,^a Gary J Noel,^b Sumati Nambiar,^c Seamus O'Brien,^d
David L Paterson,^e Julia A Bielicki,^f Michael Sharland^f & John S Bradley^g

^a Sydney Institute for Infectious Diseases, University of Sydney, Sydney, Australia.

^b Great Falls, United States of America (USA).

^c Child Health Innovation and Leadership Department, Johnson and Johnson, Raritan, USA.

^d Global Antibiotic Research and Development Partnership, Geneva, Switzerland.

^e University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, Herston, Australia.

^f Centre for Neonatal and Paediatric Infection, City St George's University of London, London, England.

^g University of California San Diego, School of Medicine, Department of Paediatrics, Division of Infectious Diseases, 3020 Children's Way, MC 5041, San Diego, California, CA 92123, USA.

Correspondence to John Bradley (email: jsbradley@health.ucsd.edu).

(Submitted: 13 December 2025 – Revised version received: 12 April 2026 – Accepted: 4 May 2026 – Published online: 27 May 2026)

Abstract

Multidrug-resistant pathogens cause severe infections with substantial morbidity and mortality in neonates, infants, and children, as they do in adults. However, the approval of therapies for multidrug-resistant infections in paediatric patients often lags years behind approval for adults, which creates an untenable situation for people who care for affected children. Many issues contribute to the current unacceptably long period between adult and paediatric new drug approval, including the requirement for sequential age group enrolment in clinical trials, the types of regulatory studies required, and a lack of alignment between regulatory authorities. To streamline paediatric drug development, more efficient approaches to investigational and approval processes that meet acceptable safety and efficacy metrics are required. For products that address an urgent unmet need in children, approval should be based primarily on matching drug exposure to levels in adults and on extrapolating safety and efficacy data from adults, where appropriate, rather than on requiring clinical trials in all paediatric age groups for each approved indication in adults. In addition, real-world and postapproval data could be used to support early, limited drug approval for paediatric patients. However, there are economic challenges in developing anti-infective drugs for paediatric populations and increased funding is needed to ensure that neonates, infants and children globally have timely access to safe, effective and life-saving therapies.

Introduction

Globally, there is an urgent need for effective antimicrobial therapy against multidrug-resistant bacteria for all paediatric age groups, especially neonates who experience the highest morbidity and mortality.^{1,2} Pathogens causing substantial morbidity and mortality in neonates, infants and children include both Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*, and Gram-negative bacteria, such as *Pseudomonas* spp., *Klebsiella* spp., *Escherichia coli*, *Acinetobacter* spp., *Burkholderia* spp. and *Stenotrophomonas* spp.³

Although the need for novel therapies to address the burden of antimicrobial resistance in children has been recognized as a priority, no accepted expedited development pathway exists. Therefore, researchers, sponsors (i.e. usually pharmaceutical companies who discover and investigate new therapies for clinical use), regulators and families involved in drug development should prioritize the unmet needs of neonates, infants and children and study new antimicrobial drugs in a transparent, efficient and collaborative manner.

The urgency of accelerating paediatric antibacterial drug development has been reflected in recent initiatives by the World Health Organization (WHO), including the paediatric drug optimization process,⁴ updated target product profiles for guiding the development of new antibacterial agents, particularly for children,⁵ and updated global research priorities for paediatric clinical trials.⁶ These initiatives emphasize regulatory harmonization requirements, prioritization of key antibacterials for children and globally coordinated, development pathways. This manuscript builds on these WHO-led programmes by outlining the practical challenges faced in expediting the provision of novel antibacterial agents for neonates and children and by proposing strategies for meeting these challenges.

Delays in access

Currently, once a new therapy has been approved for adults, it may be several years before approval is granted for children.¹ Moreover, there are often additional delays for neonates and young infants, who are usually studied after older children. Despite efforts by regulatory authorities and WHO to promote the development of paediatric antibacterials, between 2000 and 2020 it took up to 7.5 years for a new parenteral antibacterial drug approved for use in adults to be approved for children by the United States Food and Drug Administration;

furthermore, during those two decades, this delay did not get shorter.^{7,8} Delays in completing the trials required by regulators arise from difficulty of enrolling children and the lack of experienced, efficient, paediatric clinical trial networks. Further, the regulatory safety and efficacy requirements imposed on relatively safe classes of antibacterials seem unnecessary for all indications in all paediatric age groups, particularly when substantial safety and efficacy data are available for adults or older paediatric age groups.⁹

Clinicians facing the difficult decision of whether to prescribe new antibacterials that have been approved for multidrug-resistant infections only in adults are also confronted by a lack of access to safety and efficacy data from paediatric drug trials. Often these data are not shared publicly after trial completion or are not reported in the peer-reviewed literature until well after the agents have been approved for adults.¹⁰ However, making these data available as soon as possible for investigators and regulators can be challenging for pharmaceutical sponsors.

Traditionally the evaluation of new antimicrobial drugs for clinical use has been the responsibility of sponsors who are required by regulators in the European Union and United States of America to assess their product in all paediatric age groups, unless specific waiver criteria are met. Paediatric trials are more costly than adult trials and are often financially borne by antibacterial development bodies such as pharmaceutical companies, governments, professional societies and foundations, often in public–private partnerships. Pharmaceutical companies, which have historically played a large role in drug development, are unlikely to recover these costs by selling drugs that are used to treat only rare multidrug-resistant infections.¹¹ Moreover, the sites conducting paediatric drug trials in cooperation with sponsors often do so at a financial loss over the duration of the study and rely on the, often voluntary, efforts of paediatricians, nurses and other care-providers to meticulously collect and report the trial data required by regulators.

Global inequalities

Access delays of new drugs are particularly concerning for low- and middle-income countries, where the need is the greatest, especially for neonates and young infants. Conducting clinical trials in these resource-constrained settings is particularly challenging given the high clinical workload, the limited research experience in some instances and the complex ethical

considerations when involving children in trials, particularly where available therapies are inadequate.^{12–15}

Strategies for expediting development

Stakeholders may accept greater risks during investigations into new therapies if the targeted infection is severe and the consequences of inadequate treatment are unacceptable. Paediatric drug development could adopt a more efficient and tailored approach if nonclinical and adult safety data and information on the safety of similar products in children are considered.⁷ Then, when the benefit–risk balance is acceptable and the need is urgent, regulatory authorities would be more likely to accept a streamlined development programme for expedited approval. The following sections outline key opportunities for improving the efficiency of paediatric antibacterial drug development, from overarching principles to practical implementation strategies (Box 1, Table 1).

Trials for expedited approval

The prime purpose of paediatric studies of new drugs is usually to address pharmacokinetics and safety. For pharmacokinetics assessments, a study design whereby a single dose or multiple doses of the investigational product are given in addition to standard-of-care therapy for any indication could be considered adequate. This approach will expedite development by not limiting pharmacokinetic assessments in children to approved adult indications, which is particularly important given the existing global variation in approval criteria for adults, such as the body site-specific indications used by the United States Food and Drug Administration and the pathogen-based indications used by the European Medicines Agency.^{16,17} Safety assessments, in contrast, may be confounded by concurrent standard-of-care antibacterial therapy. Potential drug–drug interactions must be evaluated, including by *in vitro* assessment, where relevant.

Comparative trials are often inefficient, unlikely to generate robust safety data in small paediatric samples and may delay access. In some cases, single-arm, open-label, noncomparative pharmacokinetic and safety studies should be considered as the basis for approval, as is the norm for other paediatric infectious disease trials, such as for tuberculosis and human immunodeficiency virus (HIV) infection.⁴ Although the inclusion of a comparator arm has advantages, obtaining robust comparative safety data is difficult when only a small

number of children are enrolled. The utility, interpretability and cost-effectiveness of larger, more complicated, comparative studies that assess both efficacy and safety is questionable, particularly where recruitment is difficult (e.g. for multidrug-resistant infections) and the primary goal is to describe pharmacokinetics and safety. In these circumstances, greater use should be made of the safety data for children available from previous trials on comparator antibacterial agents and from the published literature rather than requiring comparative trials for all products.¹⁸

Simultaneous investigation

Accurate pharmacokinetics data and an understanding of drug exposure are essential before conducting studies of clinical efficacy, but the traditional approach of completing pharmacokinetic studies sequentially in decreasing paediatric age cohorts delays the access to novel antimicrobials.¹⁸ This lengthy process may not be needed, especially for classes of antimicrobial drug that have predictable pharmacokinetics and a well-established safety profile. Where appropriate, simultaneous pharmacokinetics investigations could be conducted across multiple paediatric age groups using weight-banded dosing, which is consistent with the WHO recommendations and practices applied in other therapeutic areas, such as the treatment of HIV infection.⁴ However, although some drugs can be investigated simultaneously in all paediatric age groups, including neonates, for others, particularly new classes of drug, data from older children should be reviewed before investigations are conducted in more vulnerable and fragile paediatric age groups.¹⁹

Extrapolating safety data

A key principle underpinning more efficient paediatric drug development is the appropriate extrapolation of safety data from adults to children. Extrapolation can help optimise the trial size required for certain products or age groups, particularly when the drug under investigation is a member of a known and well-studied class of antibacterials, such as β -lactam- β -lactamase inhibitor combinations.¹⁸ Small clinical trials involving four to six subjects per age group could be used to supplement the extrapolation of efficacy data from adults to children, thereby helping achieve approval for children and neonates. There may be some concerns about using this approach for new classes of antimicrobial with less information available for either adults or children or with known toxicities in children (e.g. tetracyclines and fluoroquinolones).²⁰

However, risks could be mitigated and safety in children could be established through postapproval studies or pharmacovigilance.^{19,21}

Extrapolating safety data from adults should consider any off-target effects of concern and the potential for age-specific or exposure-specific toxicities. For some drugs, the risks may be greater in neonates and young infants than in older children or adults; for example, central nervous system exposure may be increased by the immaturity of the blood–brain barrier and the immature neonatal brain may be more susceptible to toxicity.¹⁷ In these circumstances, additional data should be collected. However, European Medicines Agency guidelines acknowledge that safety profiles in adults and children are expected to be similar for similar systemic exposures, which supports the extrapolation of safety data from adults to children.¹⁷ In addition, the International Council for Harmonisation’s 2024 E11A paediatric extrapolation supports a structured and continuum-based approach to the extrapolation of safety data.²² This guidance also recommends using modelling and targeted data collection to help address uncertainty and devise more efficient paediatric trial designs.

Extrapolating efficacy data

Paediatric drug development could also be streamlined by extrapolating efficacy data from adults to children for matched drug exposure. Modelling or simulating the relationships between drug exposure and clinical or microbiological outcomes could reduce the number of children that need to be enrolled in trials to validate exposure levels, thereby expediting the approval of new drugs. Nevertheless, paediatric antibacterial trials should be designed primarily to assess pharmacokinetics and safety, rather than efficacy. For most infectious diseases, adult exposure data, along with associated microbiological and clinical efficacy data, can be used to support paediatric drug approval. However, pathogen characteristics, their pathophysiology and the clinical presentation must be considered to address important differences between adults and children or between paediatric cohorts.^{16,17} For example, bacterial sepsis is specific risk for neonates and young infants because of differences in clinical and microbiological responses to particular drug exposure levels, thereby making it difficult to reliably extrapolate data from adults or older children.²³

Adolescents in adult trials

When adequate data from early phase studies in adults are available to assess the risks and benefits of a new drug, efforts should be made to enrol adolescents in adult phase-3 trials or in parallel cohorts. This approach is consistent with regulatory guidance, has been successfully implemented in other therapeutic areas and can lead to the simultaneous approval and labelling of a new drug for use in both adults and children as young as 12 years of age.^{16,17} Moreover, the early availability of data on adolescents can enable studies in younger children to start sooner.

Neonates

Neonates, including premature neonates, and infants younger than 3 months require additional considerations due to their particular physiology and to the high unmet clinical need for novel antimicrobials in this age group. The current substantial delay in addressing this population's needs is unacceptable and results in a high number of unnecessary deaths.¹ During the first weeks of life, the pharmacokinetics and safety of antimicrobial drugs can be extensively affected by rapidly evolving differences in the distribution of drugs between tissues and by the maturational development of renal and hepatic clearance.²⁴

In neonates, assessment of toxicity is challenging because physical examination is limited and blood sampling difficult. In addition, the long-term impact of adverse events following drug exposure, which may not be apparent at the time of administration, may be difficult to determine. Further, the immaturity of the immune system during the first few months of life can also affect the assessment of efficacy because clinical outcomes depend on both antimicrobial drug activity and the host immune response.²³ Finally, effectiveness may be influenced by obstacles to drug administration, including the limited availability of age-appropriate formulations and variations in drug delivery, particularly for critically ill neonates.

Consequently, pharmacokinetics, safety, formulation, dosing and efficacy of drugs must be addressed across a wide range of gestational and chronological ages. The feasibility of different administration methods must also be considered to ensure optimal uptake and real-world effectiveness. For drug classes for which substantial safety and efficacy data are available for older children and adults, such as β -lactam- β -lactamase inhibitor combinations, approval could be based on data from fewer neonates. However, this approach might not be appropriate for new molecular entities.

Expedited approval pathways

Drug development programmes for specific paediatric groups could be streamlined, similar to the limited approvals granted for adults, provided safety and efficacy limitations in children is clearly understood.¹⁸ Additional evidence could be systematically collected from publications, postmarketing reports and databases, with postapproval safety reporting helping to address the initial data gaps. Further, modelling and simulation, extrapolation and the use of real-world data are critical for complementing data from clinical trials on the benefit–risk balance of a product. Although real-world data have limitations, they provide useful information on safety, rare adverse events, real-world effectiveness and dosing patterns in clinical practice. As novel agents may be used infrequently in early postapproval settings, real-world data have to be interpreted with caution and their ability to generate robust or generalizable evidence may be limited.²⁰ Furthermore, the risks and benefits of expedited approval should be carefully considered for high-risk populations, such as neonates. Targeted safety evaluations and robust postmarketing surveillance are necessary to ensure that access to life-saving therapy is balanced by careful and ongoing risk assessment.

Off-label antimicrobial use

The off-label use of new antimicrobial drugs in the period between adult and paediatric approval can provide an important source of real-world evidence that complements structured data collection through clinical trials and postmarketing surveillance. Clinical information about dosing and the risks and benefits of off-label use is critical before paediatric approval, particularly when children cannot be enrolled in a clinical trial for these agents and no other treatments exist.

Regulatory alignment

Regulatory requirements for paediatric drug development should be harmonized between the European Medicines Agency, the United States Food and Drug Administration and other regulatory authorities to streamline global drug development.¹⁸ Aligning paediatric investigational protocols would also facilitate timely planning and execution. Ideally, high-quality, paediatric data generated in one region should support regulatory approval in other regions. Existing pathways for regulatory national cooperation should be expanded, especially where there is an urgent need.¹⁷

The development of international, standardized, paediatric drug investigational protocols for commonly studied indications (e.g. skin infections, urinary tract infections and pneumonia), as often used in adult drug development, could help streamline regulatory processes in individual countries and make the approval and conduct of paediatric clinical trials more efficient. In addition, standard protocols would facilitate pooled data analysis, thereby increasing understanding of the safety, efficacy and pharmacokinetics of drugs across all paediatric age groups. As countries beyond the European Union or the United States may submit paediatric approvals early, regulatory alignment before paediatric trials is critical to ensure the studies meet the regulators' requirements.¹⁹

Early submission of trial data

Given that the approval and labelling of some novel antimicrobials (e.g. bedaquiline and HIV drugs) is carried out in a sequential, age-stratified manner, it is important that the data from older age cohorts of children used to support approval are submitted as soon as possible because early submission can be very effective for ensuring drug labelling is updated for older children while clinical trials in younger age groups, including neonates, are still ongoing.^{6,9} Although multiple submissions of data may be burdensome for sponsors and regulatory agencies, approval and labelling updates can be timelier and, in any case, multiple submissions are needed to ensure the appropriate use of some new antibacterials.¹⁸ Moreover, regulators considered this an acceptable approach.

Expanding clinical trial networks

In the United States, there are no successful, free-standing, paediatric trial networks for investigating drugs for regulatory approval. Setting up paediatric investigation sites is costly and time-intensive often repeated for each new drug developed. For example, some phase-2 and -3 studies of new paediatric antimicrobial drugs required up to 50 clinical trial sites worldwide, and it takes years to identify, contract and delivering training at the sites. For most antimicrobial drug trials, the average number of subjects enrolled at each site is small. In our experience with facilitating studies involving children, two or fewer children may be enrolled at each site and as many as half the sites involved may not enrol a single patient.²⁵ Consequently, trial costs per evaluable child can be substantially greater than the cost per adult enrolled in comparable trials, which reflects the complexity of, and resources required by,

paediatric studies. Rather than being a profitable investment, these trials are usually a financial liability that the sponsor must accept to comply with the drug development programme required.

In contrast, there are paediatric clinical trial networks outside the United States, such as the African–European SNIP-AFRICA collaboration,²⁶ the Paediatric European Network for the Treatment of AIDS and Infectious Diseases,²⁷ and initiatives by the Global Antibiotic Research and Development Partnership.²⁸ However, attempts to create sustainable paediatric trial site networks for antibacterial drug development have been hampered by limited support for full-time academics and health workers to be involved and the high cost and resources required to recruit and sustain the personnel needed. Although funding mechanisms for clinical trial networks exist globally, securing reliable, sustainable funding (e.g. from sponsors, governments or nongovernmental organizations) remains a major barrier.

Public–private collaborations can play a role in establishing sustainable global paediatric trial networks, but adequate funding for capacity-building and the establishment of networks is essential, particularly where unmet needs for novel antimicrobials are greatest. In addition, the efficient implementation of clinical trials and the generation of reliable data depend on strengthening data surveillance by providing adequate funding and infrastructure and on improving the standardization of key variables, such as definitions of the populations studied, inclusion and exclusion criteria, pharmacometrics for drug exposure, clinical and laboratory assessments, adverse events, and short- and long-term treatment outcomes.

Trial site contracting and funding

The clinical trial contracting process is often complex and time-consuming and varies greatly across sites and regions, thereby contributing to delays in activating sites and initiating trials. In many resource-constrained, health-care settings, the limited availability of dedicated research staff to assist in executing contracts can delay the implementation of trials where they are most needed. Contracts are important because they specify the obligations of sponsors, investigators and sites and define publication and intellectual property rights. However, their implementation could be simplified by the creation of a standardized contract to be shared with all research sites, which would increase transparency and promote dialogue between sites to ensure a successful, collaborative relationship. Standardization could also expedite the research

process and the publication of results. Information on budgeting should be transparent, standardized and shared between sites and sponsors or clinical research organizations to ensure that trials are conducted appropriately and no site makes a profit or loss.

Engaging community stakeholders

In addition to sponsors and regulators, community stakeholders, such as trial investigators, health workers and parents, should be fully engaged in the approval and labelling of novel antibacterials to treat drug-resistant infections. Early engagement of stakeholders, starting at protocol design, help ensure understanding of the trial, smooth enrolment and successful completion. Early has been shown to make recruitment easier, to ensure that study procedures and the overall conduct of the trial are acceptable in a paediatric setting, and clarifies the risks and benefits associated of a child's participation.^{29,30}

Conclusion

All stakeholders involved in promoting the health of neonates, infants and children need to collaborate to address the challenges of paediatric drug development. The study populations required for paediatric drug trials could be reduced by ensuring pharmacokinetic and safety investigations of new antibacterial drugs are performed efficiently and by designing clinical trials to take advantage of extrapolated efficacy data from adult trials, where appropriate. In addition, real-world and postapproval data could be used to support early, limited drug approval to enable prompt paediatric access to critically needed antibacterials active against multidrug-resistant pathogens. Nevertheless, we acknowledge that there are economic challenges in developing anti-infective drugs for all paediatric populations. Increased funding is needed from global governments, industry and philanthropic sources, along with statutory financial incentives for novel paediatric antibacterials, to ensure that neonates, infants and children in both well-resourced and resource-constrained health-care settings have timely access to safe, effective and often life-saving therapies.

Acknowledgments

Phoebe CM Williams is also affiliated with the School of Women and Children's Health, University of New South Wales, Australia and the Department of Infectious Diseases, Sydney Children's Hospital Randwick, Australia. Julia A Bielicki is also affiliated with the Paediatric Research Centre, University Children's Hospital Basel, Switzerland.

Competing interests:

None declared.

References

1. Williams PC, Qazi SA, Agarwal R, Velaphi S, Bielicki JA, Nambiar S, et al. Antibiotics needed to treat multidrug-resistant infections in neonates. *Bull World Health Organ.* 2022 Dec 1;100(12):797–807. <https://doi.org/10.2471/BLT.22.288623> PMID:36466207
2. Piddock LJV, Alimi Y, Anderson J, de Felice D, Moore CE, Røttingen JA, et al. Advancing global antibiotic research, development and access. *Nat Med.* 2024 Sep;30(9):2432–43.
3. Naghavi M, Vollset SE, Ikuta KS, Swetschinski LR, Gray AP, Wool EE, et al.; GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet.* 2024 Sep 28;404(10459):1199–226. [https://doi.org/10.1016/S0140-6736\(24\)01867-1](https://doi.org/10.1016/S0140-6736(24)01867-1) PMID:39299261
4. Paediatric drug optimization for antibiotics: meeting report, 30 November, 5–7 December 2022. Geneva: World Health Organization; 2023. Available from: <https://iris.who.int/bitstream/handle/10665/366533/9789240068933-eng.pdf?sequence=1> [cited 2024 May 10].
5. Target product profiles for new antibacterial agents. Severe multidrug-resistant Gram-negative infections, antibiotic-resistant Gram-positive infections in immunosuppressed and critically ill patients, and community-acquired and health care-associated bacterial meningitis. Geneva: World Health Organization; 2026. Available from: <https://iris.who.int/server/api/core/bitstreams/aba1b95b-1183-4c27-8603-d9c306a0d57d/content> [cited 2026 May 17].
6. The future of paediatric clinical trials – setting research priorities for child health. Technical report. Geneva: World Health Organization; 2025. Available from: <https://iris.who.int/server/api/core/bitstreams/c26226c0-e533-46c3-8639-ed8b081223c0/content> [cited 2026 May 17].
7. Accelerating optimal approval of priority formulations for antibiotic use in children: meetings report, 7 December 2023 and 19–20 March 2024. Geneva: World Health Organization; 2024 Available from: <https://www.who.int/publications/i/item/9789240103351> [cited 2026 May 17].
8. McNeeley D, Noel G, Bradley JS, Nambiar S. The need for continued vigilance to ensure that children of all ages are appropriately prioritized in the development of new antibacterial agents. Abstract 5094. ASM Microbe, Washington, DC, United States, 9–13 June 2022. Chicago: CTI Meeting Technology; 2022. Available from: <https://www.abstractsonline.com/pp8/#!/10522/presentation/5094> [cited 2026 May 17].

9. Noel GJ, Nambiar S, Bradley J; Clinical Trials Transformation Initiative's Pediatric Antibiotic Drug Development Program. Advancing pediatric antibacterial drug development: a critical need to reinvent our approach. *J Pediatric Infect Dis Soc.* 2019 Mar 28;8(1):60–2. <https://doi.org/10.1093/jpids/piy001>
PMID:29438520
10. Hovinga C, McNeeley D, Bradley J, Nambiar S, Noel G. Characterization of published information that is available for informing treatment of children with serious infections with antibacterials that have been approved for use in adults but have yet to be labeled for use in children. Abstract 5095. *ASM Microbe*, Washington, DC, United States, 9–13 June 2022. Chicago: CTI Meeting Technology; 2022. Available from: <https://www.abstractsonline.com/pp8/#!/10522/presentation/5095> [cited 2026 May 17].
11. Årdal C, Balasegaram M, Laxminarayan R, McAdams D, Outtersson K, Rex JH, et al. Antibiotic development – economic, regulatory and societal challenges. *Nat Rev Microbiol.* 2020 May;18(5):267–74. <https://doi.org/10.1038/s41579-019-0293-3> PMID:31745330
12. Bielicki JA, Sharland M, Heath PT, Walker AS, Agarwal R, Turner P, et al. Evaluation of the coverage of 3 antibiotic regimens for neonatal sepsis in the hospital setting across Asian countries. *JAMA Netw Open.* 2020 Feb 5;3(2):e1921124. <https://doi.org/10.1001/jamanetworkopen.2019.21124>
PMID:32049298
13. Johnson J, Robinson ML, Rajput UC, Valvi C, Kinikar A, Parikh TB, et al. High burden of bloodstream infections associated with antimicrobial resistance and mortality in the neonatal intensive care unit in Pune, India. *Clin Infect Dis.* 2021 Jul 15;73(2):271–80. <https://doi.org/10.1093/cid/ciaa554> PMID:32421763
14. Peters L, Olson L, Khu DTK, Linnros S, Le NK, Hanberger H, et al. Multiple antibiotic resistance as a risk factor for mortality and prolonged hospital stay: a cohort study among neonatal intensive care patients with hospital-acquired infections caused by Gram-negative bacteria in Vietnam. *PLoS One.* 2019 May 8;14(5):e0215666. <https://doi.org/10.1371/journal.pone.0215666>
PMID:31067232
15. Dickson BFR, Harrison M, Villanueva-Uy MET, Putri ND, Adrizain R, Kartina L, et al.; NeoSEAP Consortium. Pathogen distribution and antimicrobial resistance among neonatal bloodstream infections in Southeast Asia: results from NeoSEAP, a multicentre retrospective study. *Lancet Reg Health West Pac.* 2025 Sep 9;62:101617. <https://doi.org/10.1016/j.lanwpc.2025.101617>
PMID:40995418
16. Development of anti-infective drug products for the pediatric population. Silver Spring: United States Food and Drug Administration; 2021. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-anti-infective-drug-products-pediatric-population> [cited 2026 Apr 11].

17. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements. Scientific guideline. Amsterdam: European Medicines Agency; 2022. Available from: <https://www.ema.europa.eu/en/addendum-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-address-paediatric-specific-clinical-data-requirements-scientific-guideline> [cited 2026 May 17].
18. Williams PCM, Bradley J, Roilides E, Olson L, Kaplan S, Lutsar I, et al. Harmonising regulatory approval for antibiotics in children. *Lancet Child Adolesc Health*. 2021 Feb;5(2):96–8. [https://doi.org/10.1016/S2352-4642\(20\)30365-5](https://doi.org/10.1016/S2352-4642(20)30365-5) PMID:33484666
19. ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population. Scientific guideline. Amsterdam: European Medicines Agency; 2018. Available from: <https://www.ema.europa.eu/en/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-scientific-guideline> [cited 2026 Apr 11].
20. Yee CL, Duffy C, Gerbino PG, Stryker S, Noel GJ. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. *Pediatr Infect Dis J*. 2002 Jun;21(6):525–9. <https://doi.org/10.1097/00006454-200206000-00009> PMID:12182376
21. Turner MA, Catapano M, Hirschfeld S, Giaquinto C; Global Research in Paediatrics. Paediatric drug development: the impact of evolving regulations. *Adv Drug Deliv Rev*. 2014 Jun;73:2–13. <https://doi.org/10.1016/j.addr.2014.02.003> PMID:24556465
22. ICH harmonised guideline: pediatric extrapolation E11A. Geneva: International Council for Harmonisation; 2024. Available from: https://database.ich.org/sites/default/files/ICH_E11A_Guideline_Step4_2024_0821.pdf [cited 2026 May 25].
23. Strunk T, Molloy EJ, Mishra A, Bhutta ZA. Neonatal bacterial sepsis. *Lancet*. 2024; Jul 20;404(10449):277–93. [https://doi.org/10.1016/S0140-6736\(24\)00495-1](https://doi.org/10.1016/S0140-6736(24)00495-1) PMID:38944044
24. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2018 Oct;58(S10) Suppl 10:S10–25. <https://doi.org/10.1002/jcph.1284> PMID:30248190
25. Bart SM, Farley JJ, Bala S, Amini T, Cox E. Geographic shifts in antibacterial drug clinical trial enrollment: implications for generalizability. *Clin Infect Dis*. 2021 Apr 26;72(8):1422–8. <https://doi.org/10.1093/cid/ciaa246> PMID:32161946
26. SNIP-AFRICA is an African–European collaboration that aims to improve the way severe infections in newborns are treated. Padova: SNIP-AFRICA; 2026. Available from: <https://www.snip-africa.org/> [cited 2026 Apr 11].

27. Paediatric European Network for the Treatment of AIDS and Infectious Diseases. Padova: Penta; 2026. Available from: <https://penta-id.org/> [cited 2026 Apr 11].
28. Global Antibiotic Research and Development Partnership. Geneva: GARDP; 2026. Available from: <https://gardp.org/> [cited 2026 Apr 11].
29. Gobat N, Slack C, Hannah S, Salzwedel J, Bladon G, Burgos JG, et al. Better engagement, better evidence: working in partnership with patients, the public, and communities in clinical trials with involvement and good participatory practice. *Lancet Glob Health*. 2025 Apr;13(4):e716–31. [https://doi.org/10.1016/S2214-109X\(24\)00521-7](https://doi.org/10.1016/S2214-109X(24)00521-7) PMID:40155109
30. Watson SE, Smith P, Snowden J, Vaughn V, Cottrell L, Madden CA, et al. Facilitators and barriers to pediatric clinical trial recruitment and retention in rural and community settings: a scoping review of the literature. *Clin Transl Sci*. 2022 Apr;15(4):838–53. <https://doi.org/10.1111/cts.13220> PMID:35037409

Box 1. Strategies for expediting paediatric antibacterial drug development

Routinely include adolescents in clinical trials

When sufficient safety data for adults are available to assess the risks and benefits of a treatment, adolescents should be enrolled in adult phase-2 or –3 trials or in a parallel cohort.

Extrapolate safety data from adult studies

Extrapolating safety data from adults to children can help reduce the trial size required for certain products or age groups, particularly when the drug being studied is a member of a known and well-studied antibiotic class (e.g. β -lactam– β -lactamase inhibitor combinations).

Streamline pharmacokinetic data collection

Obtain pharmacokinetic data from studies in which investigational products are given in addition to standard-of-care treatment, for any indication.

Use noncomparative trials

Consider using single-arm, open-label studies in children for licensing and approval purposes rather than large, standard studies with comparator treatments, for which recruitment is difficult.

Strengthen global paediatric trial networks

Fund public–private partnerships that support global, paediatric, clinical trial networks investigating novel antibacterial drugs in neonates and children.

Table 1. Strategies and actions for expediting the development of new agents to treat multidrug-resistant infections in children and neonates

Strategy	Action	Advantages	Challenges and risks	Priority for implementation
Global regulatory alignment and harmonization	Align requirements across regulatory authorities and policy-making bodies	(i) Reduces the risk of duplication and unnecessary additional trials; (ii) streamlines drug development; and (iii) improves global access to new drugs	Requires coordination across jurisdictions that may have different regulatory priorities	High
Expanded paediatric clinical trial networks	Develop sustainable, well funded, international networks to support efficient trial implementation in both resource-rich and resource-constrained health-care settings	(i) Makes trial recruitment easier; (ii) builds capacity for conducting trials; (iii) enhances data quality; and (iv) ensures clinical findings are generalizable across all paediatric populations	Requires substantial, sustainable funding and coordination to ensure gains in capacity-building are maintained	High
Noncomparative trial designs	Conduct single-arm, open-label pharmacokinetic and safety studies rather than small, underpowered comparative trials	(i) Increases trial feasibility; (ii) avoids inefficient trials; and (iii) reduces delays in implementation	Comparative safety data are limited	High
Extrapolation of efficacy data from adults	Use adult efficacy data to expedite paediatric drug approval	(i) Avoids unnecessary efficacy trials; (ii) widely accepted by regulators; and (iii) efficient	May not be appropriate for all infections, particularly where the disease pathophysiology differs between adults, children and neonates	High
Extrapolation of safety data from adults	Use existing adult and paediatric safety data, especially for known drug classes (e.g. β -lactam- β -lactamase inhibitor combinations)	(i) Reduces the need for large paediatric trials; and (ii) enables earlier approval	Close postmarketing monitoring is required to detect unforeseen toxicity risks, particularly for neonates	High
Simultaneous pharmacokinetic investigations across paediatric age groups	Conduct pharmacokinetic studies in multiple paediatric age groups concurrently (e.g. using weight-banded dosing) rather than sequentially	(i) Avoids delays inherent in age de-escalation; and (ii) accelerates neonatal access to drugs	(i) Requires careful safety oversight; and (ii) may not be appropriate for novel drug classes	High

Inclusion of adolescents in adult trials	Enrol adolescents in phase-3 adult trials, when appropriate, to enable earlier drug labelling for children	(i) Enables near-simultaneous approval for adolescents and adults; and (ii) reduces trial duplication and the need for slow age de-escalation trials	Requires the alignment of regulatory and ethical frameworks, as well as the willingness of site investigators to enrol younger cohorts	High
Expedited conditional approval pathways	Allow rapid drug approval for conditions with a high unmet need for novel antimicrobials and support approval through postmarketing studies	Enables timely access to life-saving therapies	(i) There may be a higher level of uncertainty about safety and efficacy at approval; and (ii) strong post-licensing, pharmacovigilance, surveillance systems must be in place	High
Strengthened data systems and standardization	Improve data collection tools, surveillance systems and the standardization of definitions of the populations studied, study inclusion and exclusion criteria, clinical and laboratory assessments, pharmacometrics for drug exposure, adverse events, and short- and long-term treatment outcomes	(i) Improves data quality; (ii) facilitates both trial implementation and postsurveillance real-world data collection; and (iii) enables pooled analyses	Requires substantial infrastructure investment and coordination	Moderate
Standardized contracts and protocols	Use harmonized contracts, trial protocols and operating procedures across trial sites and regions	(i) Reduces delays in site activation and study commencement; and (ii) improves transparency and efficiency	May be difficult to implement across diverse legal and institutional systems	Moderate
Real-world data use	Use observational data, including data attained from off-label prescribing, to complement clinical trial data on safety and effectiveness	(i) Reflects real-world drug use; and (ii) increases pre- and post-approval evidence generation	(i) Information on off-label use may not always be published; (ii) data available for novel agents may be limited; and (iii) prescribing bias and confounding is possible in certain patient populations	Moderate