Harmonising Regulatory Approval for Antibiotics in Children

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Antimicrobial resistance (AMR) represents a substantial threat to the Sustainable Development Goals (SDGs) with a significant impact on the health of children worldwide.1,2 However, very few trials for new antibiotics have been conducted in children to inform the optimal treatment of multidrug-resistant (MDR) infections. The current drug regulatory framework has evolved from a system that (rightly) aimed to protect children, yet remains governed by interpretation of laws established in response to historical incidents involving agents that caused harm.3 This approach, particularly for medicines from well-established classes with a long experience of safe use in children (such as β-lactam penicillins), now unnecessarily complicates the process of paediatric antibiotic development and is one of the many barriers to children with MDR infections being appropriately treated with licensed drugs.

Currently, two regulatory authorities oversee the development of most new antibiotics for children. In the European Union, a paediatric investigation plan (PIP) is submitted to the European Medicines Agency (EMA). In the US, a paediatric study plan (PSP) is required under the Food and Drug Administration Safety and Innovation Act (FDASIA).4 While co-ordination between these bodies regularly occurs, progress in the harmonisation of study design appears to have stalled.

Both regulators accept that efficacy can be extrapolated from adult studies, with pharmacokinetic (PK) studies designed to achieve similar drug exposure in children as in adults. Both regulators accept simultaneous cohort recruitment to single-dose PK studies across all ages. With optimised sampling designs based on extrapolation from adults, this data can usually be achieved with the recruitment of 40-50 children (aged 0-18 years).

However, the recent draft FDA guidance of anti-infective development in the pediatric population continues to require the *de-novo* generation of primary safety data in children obtained in randomised trials including a standard-of-care (SOC) arm.5 The FDA also only accepts the recruitment of children with the clinical indication for which the agent is licensed in adults, often restricted to complicated urinary tract infections – despite the very short hospital stay this diagnosis requires in children and the limited clinical need for new agents for this indication – resulting in challenges in clinical justification and trial recruitment, especially in the COVID-19 era.6 By contrast, the EMA has broadly accepted that both efficacy *and safety* can be bridged from adult studies for well-established classes of antibiotics and children can be recruited into PK studies with any relevant clinical infection.

There has been a considerable change in the requirements by regulators for paediatric antibiotic studies, responding appropriately and rapidly to the continued challenges involved in drug development. Previously, the FDA required sample sizes of 100-200 children randomised 1:1 between the active drug and a SOC comparator arm. However, these numbers have steadily reduced, and recently approved study designs now have 4:1 randomisation of active drug to SOC arms, with a total recruitment target of 50-60 children in the multi-dose component of the programme. Different SOCs are accepted between centres, resulting in potential safety signals in the active arm being compared to only 10-15 children receiving multiple SOC regimens. This results in the anomalous position where the numbers of children recruited results in sample sizes far too small to detect novel safety signals with any valid level of precision.

Antibiotic-related toxicities in children are highly predictable from adult studies, and the sample size required to identify (with any reasonable statistical power) a novel safety signal in paediatric trials has recently been determined as considerably higher than most approved PSPs.7 Due to the divergent regulatory approaches between the EMA and FDA, some pharmaceutical companies are establishing two separate global registration trials for new antibiotics for children (one for each regulatory authority), at significant expense and complexity, potentially delaying registration and impacting on the delivery of paediatric drug development programs.8 By contrast, there have been significant advances in streamlining antibiotic regulatory trials for adults, further shortening the approval process for this age group.9 There is therefore currently a delay of around a decade between the time antibiotics are licensed for use in adults before they are licensed in children.7

Currently, only five new antibiotic trials to address MDR infections are actively recruiting children (ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam and cefiderocol), of which only two (ceftazidime-avibactam and imipenem-relebactam) include neonates, despite the significant burden AMR causes in this population.10 We suggest there is now a clear need to harmonise regulatory approval requirements for new antibiotics in children (see box). Without global collaboration and an enhanced focus on licensing new antibiotics tackling the global burden of MDR infections in children, the SDGs are unlikely to be achieved by 2030.

**Recommendations to achieve harmonised and expedited regulatory approvals for new antibiotics for use in children**

1. There should be recognition that for well-established classes of antibiotics such as β-lactam/β-lactam inhibitor combinations, single and multidose PK and safety studies can provide the basis for licensure.
2. Randomised trials with SOC comparator arms should not be required for licencing well-established classes of antibiotics with a well-established safety profile.
3. Recruitment of children into pharmacokinetic and safety studies should allow for inclusion of patients with *any* relevant bacterial infection, rather than restricting enrolment only to those with the adult licensed indication for the antibiotic under investigation. This will enable investigation of a more generalisable patient population and facilitate recruitment, to ensure appropriate sample sizes with adequacy to detect safety signals and accurately predict pharmacokinetic parameters are enrolled.
4. Wherever possible, the goal should be for the FDA and EMA to agree to the development of a single study master protocol for new antibiotics, based on single and multi-dose pharmacokinetics, that requires only one global trial for recruitment and registration across all licensing authorities.
5. A clear focus on reducing the time between new antibiotics being licensed for use in adults and children is necessary. An achievable goal of paediatric licences being issued within five years of the adult licence should be established.

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