Antimicrobial resistance among children in Africa: need for paediatric clinical trials

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Expert Review of Anti-infective Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>ERI-2020-ST-0075.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Editorials</td>
</tr>
<tr>
<td>Keywords:</td>
<td>Antimicrobial resistance, Antimicrobial stewardship, Africa, Children, Clinical trial, Neonate, Paediatric</td>
</tr>
</tbody>
</table>
Abstract

Clinical trials are the gold standard for generating evidence-based knowledge in medicine; however, few are conducted in children despite this population having the highest prevalence of antimicrobial-resistant (AMR) infections. Between January 2010-Dec 2019, antimicrobial clinical trials registered on clinicaltrials.gov accounted for 4.0% of all interventional clinical trials, with paediatric antibacterial clinical trials on the African continent making up <1%. The African paediatric population (particularly neonates and infants) have the highest prevalence of AMR infections, but receive the lowest investment and participation in clinical research for antibacterial agents. African clinician investigators, who are most familiar with the local disease burden and health system challenges, are best suited to lead research efforts to generate guidance for therapy of paediatric infections in Africa in the era of AMR.
Clinical trials are the gold standard for generating evidence-based knowledge in medicine. A disproportionately small number of clinical trials are conducted in children, a unique population who require age- and development-specific treatments. The rise in prevalence of antimicrobial resistant (AMR) – specifically antibacterial resistant – paediatric infections in both community and hospital settings in Africa [1, 2] has not been matched by increases in access to effective antimicrobial therapy. In many low-resource settings, empirical antimicrobial therapies are no longer effective, and therapeutic options for AMR pathogens are either unaffordable or unavailable locally.

Given the dearth of therapeutic options for paediatric AMR infections in low-resource settings, we evaluated trends in the proportion of paediatric trials in Africa, with a specific focus on antibacterials. We reviewed all interventional clinical trials involving antibacterial agents registered on clinicaltrials.gov over a ten-year period (January 2010-Dec 2019), in children up to 17 years of age. We excluded studies of antimicrobial prophylaxis, non-systemic, non-antibacterial, and antitymbocellular agents, and trials of unknown status or withdrawn before enrollment. Each site-country in multi-site antibacterial trials was considered a unique study. Full names were used to approximate the investigator genders. The overall principal investigator was determined for multi-site studies and a study was considered to be African-led if any overall principal investigator was from an African institution.

We identified 224,297 studies, of which 141,118 (62.9%) were interventional clinical trials. Antimicrobial clinical trials accounted for 4.0% (5,600/141,118), with paediatric involvement in 0.8% of interventional trials (1,121/141,118). Less than 10% (111/1,121) of paediatric antimicrobial clinical trials were/are being conducted in Africa. Of these, 104 (93.7%) had a sponsor and/or principal investigator from outside the African continent. We
classified 47-46 as antibacterial trials in Africa, of which seven were African-led (15%) and four of those (57%) had a female principal investigator.

Between 2010-2014 and 2015-2019, the number of registered studies increased 32.9%, interventional clinical trials increased 50.1%, and paediatric interventional clinical trials increased 47.7% (Figure 1A). By comparison, paediatric interventional antimicrobial clinical trials increased 25.6% over this same period (Figure 1B). The most common infectious conditions evaluated were trachoma, malnutrition, diarrhoea and pneumonia. The most common antibacterial classes involved were macrolides (azithromycin, 19/46 (41%)), and penicillins (amoxicillin, 11/46 (24%)). Although in Africa the number of paediatric interventional antibacterial clinical trials roughly doubled during this timeframe, the 47-46 trials that were conducted over a 10-year period equates to 0.8% of all interventional antimicrobial clinical trials registered.

These data highlight several issues: firstly, though the number of clinical trials conducted globally is increasing, the number of antimicrobial clinical trials conducted in settings where burden of infectious diseases is highest remains disproportionately low. This may reflect the lack of discovery of new antibiotic classes in the last 30 years or limited capacity to conduct such trials where the burden of infectious diseases is highest. Secondly, while half of the world’s 5.2-9.2 million under-five deaths occur in Africa, most attributable to infections, paediatric antibacterial clinical trials on the African continent account for <1% of all interventional clinical trials. Thirdly, whereas 44% of all child deaths now occur in the neonatal period, only two antibacterial clinical trials were specifically designed to target neonates. Finally, non-African institutions sponsor and/or are lead investigators in the vast majority of paediatric antimicrobial clinical trials conducted in Africa.
Despite the history and complexity of conducting clinical trials on the continent, from basic infrastructure to questionable ethical practices\cite{5-7,6-8}, the foundation for clinical trials in Africa has improved immensely. Capacity-building initiatives take time to bear fruit, and developing research infrastructure is a long-term investment. African-led clinician scientists are best placed to ask relevant research questions in their local setting, and should be supported and empowered to conceive, design, and lead studies to answer the research questions derived from their settings\cite{8,9}. This would identify context-based solutions adaptable to different parts of the continent.

This study has several limitations. Firstly, we only reviewed clinical trials registered on clinicaltrials.gov, which would have missed non-listed research and protocols registered only on local/national regulatory websites. Secondly, though an antibacterial trial may have involved multiple countries, each country involved was counted as a unique study. If anything, this approach would have led to an overestimation of the representation of African antibacterial clinical trials in the global context.

AMR is a growing public health crisis disproportionately affecting African countries where infection burden is high but access to effective therapies is severely limited. The African paediatric population (particularly neonates and infants) have the highest prevalence of AMR infections, but receive the lowest investment and participation in clinical research for antibacterial agents. We argue that African clinician investigators, who are most familiar with the local disease burden and health system challenges, are best suited to lead research efforts to generate guidance for therapy of paediatric infections in Africa in the era of AMR.
Declaration of interests

PI has received grants from the Bill & Melinda Gates Foundation and European and Developing Countries Trials Partnership outside of the submitted work. BOO has received personal fees from Pfizer and non-financial support from Sanofi outside of the submitted work. The other authors have no conflicts of interest.

Contributorship statement

PI conceived, conducted data collection and analysis, and wrote the first draft. All authors reviewed, edited, contributed to, and approved the final draft.
References


**Describes trends in pathogen resistance to empirical first- and second-line antimicrobials at a tertiary hospital in Malawi over a twenty year period, where increases are most rapid among children <5 years and particularly young infants.**


**Results from a randomised clinical trial comparing equivalence of antimicrobial regimens in low resource settings in Africa.**