Article

PAMJ One Health

Perspective

New advances in paediatric drug-resistant tuberculosis

Sheetal Harichander, Varsha Bangalee, Frasia Oosthuizen

Corresponding author: Sheetal Harichander, Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa. sheetal.harichander@gmail.com

Received: 24 Jan 2025 - **Accepted:** 23 Feb 2025 - **Published:** 02 Apr 2025

Keywords: Drug-resistance, tuberculosis, paediatrics, treatment, dosage forms

Cite this article: Sheetal Harichander et al. New advances in paediatric drug-resistant tuberculosis. PAMJ-One Health. 2025;16(11). 10.11604/pamj-oh.2025.16.11.46666

Available online at: https://www.one-health.panafrican-med-journal.com/content/article/16/11/full

New advances in paediatric drug-resistant tuberculosis

Sheetal Harichander[1,&], Varsha Bangalee[1], Frasia Oosthuizen[1]

[1]Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

[&]Corresponding author

Sheetal Harichander, Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

Abstract

Drug-resistant (DR) tuberculosis (TB) in children presents unique treatment challenges due to limited paediatric formulations, drug toxicity concerns, and gaps in clinical research. Recent advancements have introduced improved diagnostic tools and novel treatment regimens, enhanced outcomes, and reduced treatment duration. This study reviews the latest developments in medicine options for paediatric DR-TB in South Africa, focusing on new and repurposed drugs. Additionally, the development of dispersible paediatric formulations has improved drug administration and adherence. Despite these advancements, challenges remain

with respect to access and the adaptation of treatment guidelines for children.

Perspective

A reflection

Tuberculosis (TB) is a preventable and typically curable disease caused by the bacterium *Mycobacterium tuberculosis* [1]. In 2022, TB was the world´s second leading cause of death from a single infectious agent, following the coronavirus disease (COVID-19), and accounted for nearly twice as many deaths as HIV/AIDS. That year, 7.5 million new TB cases were reported globally, the highest number since the World Health Organization (WHO) began tracking TB in 1995 [1]. This figure likely includes a backlog of cases from previous years, as the COVID-19 pandemic disrupted healthcare services and delayed diagnoses and treatments. According to the WHO´s Global TB Report, 12% of TB cases in 2022 occurred in children aged 0-14 years. Additionally, an estimated 410,000 people worldwide developed drug-resistant (DR) TB that same year [1].

Of the estimated 1.2 million children under the age of 15 who develop TB each year, only about one-third receive a diagnosis and are treated [2]. Even more concerning is that, of the 30,000 children believed to have multidrug-resistant (MDR) TB caused by organisms resistant to at least isoniazid and rifampicin, only around 5,000 receive treatment annually [2]. South Africa (SA) is listed as one of the high-burden countries for TB, human immunodeficiency virus HIV-associated TB, and Multi-drug Resistant MDR/Rifampicin Resistant (RR) TB [1]. However, SA has increased efforts to locate individuals with undiagnosed disease and initiate treatment. Furthermore, the country has been instrumental in providing evidence and research in terms of HIV, TB, and DR-TB to the WHO.

Though children with DR-TB have better treatment outcomes than adults [3,4], many children struggle during treatment due to the limited availability of paediatric formulations of antitubercular medication [5]. Childhood TB and DR-TB have previously been treated through the estimation of paediatric doses by the crushing of adult tablets and opening of capsules [6]. This could result in incorrect dosing, which may lead to prolonged hospitalization and require significant staff time for preparing and administrating medication [6,7]. This impacts treatment adherence in the population, which leads to treatment failure [7-10]. Some of the factors that impact adherence in children include the lack of paediatric formulations, pill burden, palatability, length of therapy, and toxicity [7-10].

Several studies conducted in SA describe the unique challenges experienced by children, caregivers, and healthcare professionals in the manipulation of solid dosage forms for the treatment of DR-TB. Wademan *et al.* described the poor overall acceptability of DR-TB in children and the negative experiences of children and caregivers [11,12]. Misra *et al.* further explored that for a child diagnosed with DR-TB, there is a lived experience of stress that impacts their physical, mental, and social well-being [13].

Closing the gaps

Following decades of limited progress, the past ten years have seen significant breakthroughs in the treatment of DR-TB in children and adolescents. These advances mark a crucial turning point in TB care, offering new hope for more effective therapies. In March 2022, the WHO recommended the use of bedaquiline and delamanid for treating DR-TB in children of all age groups [14]. These new and repurposed drugs offer promising opportunities to shorten the traditionally lengthy treatment duration and reduce reliance on injectable drugs, as well as drugs associated with severe side effects and drug interactions.

The Stop TB Partnership's Global Drug Facility (GDF), acknowledged as the world´s largest supplier of quality-assured TB medications, has

taken significant steps to include child-friendly formulations in its product portfolio. These formulations include second-line TB drugs such as bedaquiline, clofazimine, cycloserine/terizidone, ethambutol, ethionamide, levofloxacin, moxifloxacin, and pyrazinamide, aiming to improve the treatment experience for children [15-17]. A presentation done at the South African Association of Hospital and Institutional Pharmacists (SAAHIP) conference in 2023 detailed the "KwaZulu-Natal Experience" with the child-friendly formulations that were donated by the GDF and received in the province in 2020 [18]. KZN received dispersible tablets of ethambutol 100mg, pyrazinamide 150mg, levofloxacin, and dispersible clofazimine 50mg. Given that these formulations were not registered in SA, the route of Section 21 was followed. This process entailed obtaining informed consent and submitting progress reports that monitored outcomes and adverse drug reactions every 6 months and at the end of treatment [18]. According to the study, 24 children in the province benefitted from this initial donation. The child-friendly formulations were well-received and tolerated by both caregivers and children. Healthcare workers noted ease of administration, better tolerability, and more accurate dosing calculations with the dispersible formulations [18].

In a presentation conducted at the 8th South African TB Conference held in June 2024, it was explained that the country received the second donation of dispersible tablets of delamanid 25mg, levofloxacin 100mg, clofazimine 100mg and linezolid 150mg in 2023 and access was expanded to the Eastern and Western Cape provinces. A third donation of bedaquiline 20mg, clofazimine 50mg, levofloxacin 100mg, and delamanid 25mg is expected this year (2024) to include two additional provinces i.e. Gauteng and Mpumalanga [19]. Table 1 provides a summary of the second-line drugs available for the treatment of DR-TB, including the dosage forms registered for use in SA and the availability of child-friendly formulations that can be procured from the STOP TB Partnership Global Drug Facility [15,17,20].

The future

Although the GDF has provided a catalogue for countries to request a donation of child-friendly formulations, access in several countries is still a challenge as indicated in a study by Buonsenso *et al.* [21] SA has received two donations from the GDF, however access has been restricted to three out of the nine provinces in the country [19]. According to the presented findings at the 8th South African TB Conference held in June 2024, uptake with the child-friendly formulations remains low in SA [19]. The country is focused on finding the missing cases of children with DR-TB and initiating treatment. More research is required into the acceptability and tolerability of these child-friendly formulations to advocate for registration in the country. Although the donation of child-friendly formulations has temporarily closed the gaps, local manufacture and registration in countries should be encouraged to ensure a sustainable supply of these formulations.

To effectively address DR-TB in children, a coordinated global effort is essential, focusing on several key areas. First, investment in paediatric research must be prioritized, with increased emphasis on paediatric-specific clinical trials to develop evidence-based treatments tailored for children with DR-TB. This includes expanding access to trials for new drug regimens and assessing the safety and efficacy of existing treatments in paediatric populations. Second, access to child-friendly drug formulations must be scaled up through collaboration between pharmaceutical companies and global health organizations, alongside streamlined regulatory processes to fast-track approvals in high-burden countries. Third, strengthening health systems in regions with high DR-TB incidence is crucial, particularly through investments in diagnostic tools and treatment infrastructure. Ensuring the availability of rapid diagnostic tools at the primary care level can significantly reduce delays in

diagnosis and treatment initiation. Finally, addressing adherence and treatment support is vital, with comprehensive systems needed to help children complete their treatment regimens. This includes providing counselling for caregivers, monitoring for adverse effects, and offering social support to help families navigate the challenges of long-term treatment.

Conclusion

While the future of DR-TB in children holds promise due to medical advancements, the global response must prioritize the unique needs of pediatric patients. Addressing the existing gaps in drug formulations, access, research, and healthcare infrastructure is essential to achieving better health outcomes and reducing the global burden of DR-TB in children.

Competing interests

The authors declare no competing interests.

Authors' contributions

Sheetal Harichander, Varsha Bangalee, and Frasia Oosthuizen conceived the study design. Sheetal Harichander wrote the draft of the manuscript with Varsha Bangalee, and Frasia Oosthuizen assisted with further drafts and revisions. All authors reviewed and approved the final version of the manuscript.

Tables

Table 1: available second-line antitubercular drugs for management of DR-TB in children

References

1. World Health Organization. Global Tuberculosis Report. 2023. Accessed on January 30, 2024.
2. Garcia-Prats AJ, Starke JR, Waning B, Kaiser B, Seddon JA. New Drugs and Regimens for Tuberculosis Disease Treatment in Children and Adolescents. Journal of the Pediatric Infectious Diseases Society. 2022 Oct 31;11(Supplement_3): S101-S109. **PubMed**| **Google Scholar**
3. Buonsenso D, Autore G, Cusenza F, Passadore L, Bonanno F, Esposito S. Multidrug-resistant tuberculosis in children: Are the same therapy options available worldwide. International Journal of Infectious Diseases. 2023 May;130 Suppl 1: S16-S19. **PubMed**| **Google Scholar**
4. Huynh J, Thwaites G, Marais BJ, Schaaf HS. Tuberculosis treatment in children: The changing landscape. Paediatric Respiratory Reviews. 2020 Nov;36: 33-43. **PubMed**| **Google Scholar**
5. Harichander S, Wiafe E, Mensah KB, Bangalee V, Oosthuizen F. The incidence of TB and MDR-TB in pediatrics and therapeutic options: a systematic review. Systematic Review. 2022 Aug 4;11(1): 157. **PubMed**| **Google Scholar**
6. Faust L, Abdi K, Davis K, He C, Mehrotra C, Stibolt E. The Roll-out of Child-friendly Fixed-dose Combination TB Formulations in High-TB-Burden Countries: A Case Study of STEP-TB. The Journal of Epidemiology and Global Health. J Epidemiol Glob Health. 2019 Sep;9(3): 210-216. **PubMed**| **Google Scholar**
7. Piñeiro Pérez R, Santiago García B, Fernández Llamazares CM, Baquero Artigao F, Noguera Julian A, Mellado Peña MJ *et al*. The challenge of administering anti-tuberculosis treatment in infants and pre-school children. pTBred Magistral Project. Anales Pediatria (Barcelona, Spain). 2016 Jul;85(1): 4-12. **PubMed**| **Google Scholar**

8. Noguera-Julian A, Buonsenso D, McKenna L, Seddon JA, Ritz N. Availability of fixed-dose, child-friendly formulations of first-line tuberculosis drugs in Europe. The European Respiratory Journal. 2021 Oct 1;58(3): 2101196. **PubMed**| **Google Scholar**
9. World Health Organization. Dosing Instructions for the use of Currently Available Fixed-dose Combination TB Medicines for Children. September 2009. Accessed on January 30, 2024.
10. World Health Organization and UNICEF. Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children. Accessed on January 30, 2024.
11. Wademan DT, Palmer M, Purchase S, van der Zalm MM, Osman M, Garcia-Prats AJ *et al*. Toward a conceptual framework of the acceptability of tuberculosis treatment in children using a theory generative approach. PLOS GlobAL Public Health. 2022 Dec 22;2(12): e0001267. **PubMed**| **Google Scholar**
12. Wademan DT, Viljoen L, Jacobs S, Meyerson K, Nombewu Y, Busakwe L *et al*Children's priorities to improve the acceptability of MDR-TB treatment: qualitative data from South Africa. International Union Against Tuberculosis and Lung Disease. 2023 Jul 1;27(7): 543-550. **PubMed**| **Google Scholar**
13. Misra S, Misra N, Seepamore B, Holloway K, Singh N, Ngozo J *et al*. "I would watch her with awe as she swallowed the first handful": A qualitative study of pediatric multidrug-resistant tuberculosis experiences in Durban, South Africa. PLoS One. 2022 Sep 16;17(9): e0274741. **PubMed**| **Google Scholar**
14. World Health Organization . WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. 2022. Accessed on April 22, 2023
15. Stop TB Partnership Global Drug Facility. Global Drug Facility Medicines Catalog January 2024. Accessed on April 22, 2023
16. Sentinel project. StopTB/GDF´s Paediatric Drug-Resistant TB (DR-TB) Donation Initiative. 2021. Accessed on April 22, 2023.
17. Harichander S, Bangalee V, Oosthuizen F. Understanding the need for paediatric DR-TB formulations in South Africa. South African Journal of Child Health. 2024 Dec 1;18(4): 160-3. **Google Scholar**
18. Misra N. “We are the Children...Hear our Voices”: Improving Access to Child-Friendly Formulations of Drug Resistance Tuberculosis Medicine: The KwaZulu-Natal Experience. Published in South African Pharmacy Journal. 2023;9(6): 56-58.
19. Misra N, Singh N, Radebe Z, Ngozo J, Furin J, Kock Y, Ndjeka N. Improving access to child friendly formulations of medicine to treat drug resistant tuberculosis in South Africa. Presented at the 8th SA TB Conference. (04-07 June 2024).
20. South African medical associatin. South African Medicines Formulary. 13 th Edition. Pages 325-340. 20.
21. Buonsenso D, Autore G, Cusenza F, Passadore L, Bonanno F, Esposito S. Multidrug-resistant tuberculosis in children: Are the same therapy options available worldwide? International Journal of Infectious Diseases. 2023 May;130 Suppl 1: S16-S19. **PubMed**| **Google Scholar**

Table 1: available second-line antitubercular drugs for management of DR-TB in children			
WHO Group	Drug	Dosage forms registered for use in SA	Availability of child-friendly formulation from Stop TB Partnership Global Drug Facility.
A. Include all three medicines, where possible.	Levofloxacin OR	250mg film-coated scored tablet; 500mg film-coated scored tablet; and 750mg film-coated scored tablet.	100mg dispersible tablet.
	Moxifloxacin	400mg tablet	100mg dispersible tablet
	Bedaquiline	100mg uncoated tablet	20mg dispersible tablet
	Linezolid	600mg tablet and 20mg/ml suspension.	150mg dispersible tablet
B. Add one or both medicines, if possible	Clofazimine	100mg capsule	50mg dispersible tablet and 50mg capsule
	Terizidone	250mg capsule	No child-friendly formulations available
C. Add to complete the regimen, and when medicines from Group A and B cannot be used	Ethambutol	400mg tablet	25mg/ml tablet and 100mg dispersible tablet.
	Delamanid	50mg film-coated tablet	25mg dispersible tablet
	Pyrazinamide	500mg uncoated scored tablet	100mg dispersible tablet
	Amikacin	IV, IM	No child-friendly formulations available
	Ethionamide	250mg film coated tablet	125mg dispersible tablet
	Para-aminosalicylic acid	4g coated granule	No child-friendly formulations available