BMC Pediatrics

RESEARCH Open Access

Manipulation of solid dosage forms for oral administration to paediatric patients for drug-resistant tuberculosis in South Africa: an observation study

Sheetal Harichander[1*], Varsha Bangalee[1] and Frasia Oosthuizen[1]

Abstract

Background Children represent a particularly vulnerable demographic in the context of drug-resistant (DR) tuberculosis (TB) due to their increased likelihood of close contact with adults diagnosed with the disease. Approximately 25 000–30 000 children develop DR-TB annually. While treatment success rates for DR-TB in children surpass those in adults, children and adolescents encounter distinct challenges throughout the diagnosis and treatment of DR-TB (including MDR-TB, Pre-XDR TB, and XDR-TB).

Aim To identify current practices in drug administration to children diagnosed with DR-TB where appropriate dosage forms are not available in South Africa.

Method An observational study was carried out at the study site to determine how medication prescribed was manipulated and administered by nursing staff to paediatric patients in the wards.

Results The observational study identified 8 drugs used in DR-TB at the study site, where some manipulation to the formulation was necessary to enable administration to paediatric patients. Linezolid and para-aminosalicylic acid are the only drugs available and registered in the South Africa in a formulation that is suitable for administration to paediatric patients. Activities carried out by nursing staff to enable the administration of DR-TB medication included cutting capsules and tablets and dissolving the tablet or capsule contents in distilled water to obtain the required suitable dose.

Discussion Lack of availability of suitable dosage forms for paediatrics patients results in several challenges, such as additional time required for drug preparation, increased time duration of medication administration, and unpalatability of drugs. These challenges may subsequently affect compliance and therapeutic outcomes of the treatment of paediatric patients, especially as outpatients.

Conclusion Research needs to focus on the development of appropriate dosage forms for the paediatric population and focus on identifying cases of DR-TB in children. This will assist in building evidence to advocate for registration of child-friendly dosage forms thereby ensuring a sustainable supply of medication.

*Correspondence:
Sheetal Harichander
sheetal.harichander@gmail.com

Full list of author information is available at the end of the article

Keywords Dosage forms, Drug-resistant tuberculosis, Paediatrics, Treatment

Background

Tuberculosis (TB) is a communicable disease and one of the leading causes of death worldwide [1]. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDSs) as per the World Health Organization (WHO) [1]. TB is caused by the bacillus, *Mycobacterium tuberculosis* (MTB), which is spread when people, infected with TB, expel bacteria into the air e.g. by coughing [1]. The disease typically affects the lungs but can affect other sites in the body [1]. TB is curable and preventable [1].

The emergence and spread of drug-resistant (DR) TB, especially multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB, presents a major challenge to global TB control. MDR-TB is defined as resistance to isoniazid and rifampicin with or without resistance to other anti-TB drugs [2, 3]. XDR-TB is caused by MTB strains that fulfill the definition of MDR-TB and which are also resistant to any fluoroquinolone and to at least one additional Group A drug (either bedaquiline or linezolid) [2, 3]. DR-TB affects children and adolescents, especially in household contacts where there is a higher risk of contracting the disease from infected adults [4–6]. Research estimates that between 25,000 and 32,000 children develop DR-TB every year, of whom < 5% receive treatment [7].

Historically, children and adolescents have not been a priority in programs for TB prevention and care [6]. This population was often thought to play only a minor role in the transmission of TB, and TB prevention and care were centred around adults [6]. The treatment of DR-TB in children is guided by the same principles and uses the same second-line drugs as in adult patients [6, 7].

There is a lack of appropriate paediatric dosage forms for DR-TB medications that are available in South Africa (SA) [7]. In recent years, child-friendly second-line TB drug formulations have gradually become more widely available [8]. The Stop TB Partnership's Global Drug Facility (GDF), the largest global provider of quality-assured TB drugs, has worked to include child-friendly formulations for bedaquiline, clofazimine, cycloserine/terizidone, ethambutol, ethionamide, levofloxacin, moxifloxacin and pyrazinamide in their catalogue, and in partnership with the Sentinel Project to support their uptake globally [8]. While countries remain where these formulations are unapproved and therefore not accessible (e.g., the European Union and SA) [8].

Orally formulated, immediate-release, adult-strength tablets are generally not designed for flexible dosing, and they are difficult to adapt to redosing based on age and/or weight, as necessary in children [7, 9]. Medicines are manipulated by the physical alteration of a dosage form to achieve the required (usually smaller) dose for administration [10]. Though this is recognized among professionals as a widespread practice, reports about manipulations of dosage forms to achieve the required dose are limited [10]. Manipulating dosage forms may be time-consuming, result in toxic or sub-therapeutic doses, and have unknown effects on the stability and bioavailability of the drug [11–13]. Drug manipulations and dose calculations may also increase the risk of administration errors [14].

The palatability of oral drugs is another factor to be considered as it can affect patient adherence [15]. Various factors influence palatability, including smell, taste, texture, and dose volume [15]. Recent studies were conducted in SA with children and their caregivers that highlighted the negative experience in terms of acceptability of DR-TB treatment [16, 17]. Nurses and caregivers also experienced challenges related to time that is needed to prepare these doses and tolerability of the children to the medication. These challenges can negatively impact adherence to therapy.

This study aimed to determine current practices in the treatment of children with DR-TB where child-friendly formulations are unavailable in Johannesburg, SA.

Methodology

Study design

This observational study was conducted at Sizwe Tropical Diseases Hospital, a specialized TB hospital located in Johannesburg, Gauteng province, SA in 2022.

Setting

SA is classified as a high TB burden country in all three of the WHO classifications – TB, TB-HIV and drug-resistant TB [1]. It is one of only 10 countries included in all three of these classifications [1]. In SA, notifications of paediatric TB cases (under 15 years) have exhibited a significant decline since 2015 [18]. This reduction could stem from either an actual decrease in case numbers or a smaller proportion of cases being detected [18]. The public health system in SA is guided by the Essential Medicines List (EML) with supporting Standard Treatment Guidelines (STGs). Although the Stop TB Partnership's GDF have included child-friendly formulations in the catalogue for some second-line TB drugs, these formulations are not registered for use in SA. SA had applied for a donation from the Stop TB Partnership's GDF but these child-friendly formulations have not been made

Table 1 Definitions of dosage form manipulations. (adapted from [20, 21])

Dosage form	Type of manipulation
Capsule	• Opened and the contents dispersed in a standard volume of distilled water. A proportion of liquid was administered.
Granules	• Opened and the contents measured before being suspended in a standard volume of distilled water, and administered.
Suspension	• Reconstituted with distilled water and a proportion administered.
Tablets	• Broken/cut and a segment administered. • Broken/cut and a segment dispersed in a standard volume of distilled water and a portion administered. • Whole tablet dispersed in a standard volume of distilled water and a portion administered.

available across all 9 provinces and remain unregistered for use. Lack of evidence of safety and efficacy in children in these formulations hinders inclusion into the National Department of Health STGs and EMLs [19].

Children with DR-TB across the province of Gauteng are referred to Sizwe Tropical Diseases Hospital to be initiated on treatment. The children are usually admitted for long periods of time due to clinical reasons or in the absence of a reliable caregiver.

Data collection

Data was obtained via direct observation of the nursing staff while they prepared antitubercular medication for administration to the children on randomly assigned days between May and June 2022. Registered drugs and their dosage forms that were available were documented. Administration of medications not manipulated were not observed.

Data analysis

Analysis of the data included comparing dosage manipulations to the patient information leaflet and paediatric dosing guidelines and a review of available literature to determine whether dosage manipulations were appropriate.

Ethics

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Reference BREC/00003668/2021) and permission to use the data was obtained from the Gauteng Department of Health and Sizwe Tropical Diseases Hospital (Reference GP202107 055). Gatekeeper permission was obtained in writing by the sister in charge. The nurses were informed about the scope of the study and gave verbal consent before being observed in the ward. Written informed consent was sought from the caregivers of the two children admitted at the time of data collection. All methods were carried out in accordance with relevant guidelines and regulations.

Table 2 DR-TB drugs and dosage forms registered for use in South Africa

Drug	Dosage form	Strength
Bedaquiline (BDQ)	Tablets	100 mg
Clofazimine (CFZ)	Gel Capsule	100 mg
Delamanid (DLM)	Tablets	50 mg
Ethambutol (ETH)	Tablets	400 mg
Ethionamide (Eto)	Tablets	250 mg
Isoniazid (INH)	Tablets	100 mg and 300 mg
Levofloxacin (LFX)	Tablets	250 mg, 500 mg and 750 mg
Linezolid (LZD)	Granules for suspension	20 mg/ml
Linezolid (LZD)	Tablets	600 mg
Moxifloxacin (MXF)	Tablets	400 mg
Para-aminosalicylic acid (PAS)	Granules	4 g
Pyrazinamide (PZA)	Tablets	500 mg
Terizidone (TRD)	Capsules	250 mg

Definitions

Manipulation of dosage forms was defined as all activities before administration that are undertaken to administer the medicine to the paediatric patient. One manipulation could comprise different steps and could, therefore, be a combination of different manipulation types. Table 1 provides the definitions for dosage form manipulations that were identified in this study.

Results

During the observation period, four nurses were observed in the ward preparing prescribed DR-TB medication to two children admitted over a period of 10 days.

Table 2 provides an overview of drugs and dosage forms registered for use in South Africa and available for the treatment of at the time of data collection in 2022.

LZD and PAS are the only drugs registered in dosage forms suitable for administration to paediatric patients in SA without further manipulations. All other drugs are only registered in tablet or capsule form and must be manipulated for paediatric administration.

The manipulation and administration of prescribed DR-TB treatment was observed in two children that were admitted at the hospital during data collection and are listed below as per Table 3.

The children are weighed once a week, on a Saturday, to aid in calculating the appropriate medication dose. The manipulation and administration of 8 prescribed drugs were observed at the study site, as per Table 4. A total of 10 manipulations and administration sessions were observed. All four nurses observed were observed during the same observation period and administered

Table 3 Children that were observed for medication administration practices

Child	Age	Gender	Weight	Date of admission/initiation	Regimen
A	23 months	Female	10.5 kg	22 February 2022	• Linezolid 8mls (160 mg) once daily • Levofloxacin 250 mg once daily • Para-aminosalicylic acid 2 g once daily • Clofazimine 100 mg three times per week on Monday, Wednesday and Friday • Terizidone 175 mg once daily • Bedaquiline 100 mg three times per week on Monday, Wednesday and Friday • Pyridoxine 12,5 mg once daily • Multivitamin 5mls once daily
B	16 months	Male	7.7 kg	24 February 2022	• Levofloxacin 150 mg once daily • Clofazimine 100 mg three times per week on Monday, Wednesday and Friday • Terizidone 125 mg once daily • Para-aminosalicylic acid 2 g once daily • Isoniazid 150 mg once daily • Delamanid 25 mg twice a day • Linezolid 6mls (120 mg) once daily • Ferrous sulphate 2,5mls once daily • Multivitamin 2,5mls once daily • Eltroxin 0,05 mg once daily • Pyridoxine 12,5 mg once daily • Folate 2 mg once daily

the prescribed treatment to both children. The most frequently manipulated dosage forms were tablets (50%, $n=4$) and capsules (25%%, $n=2$).

BDQ, CFZ, DLM, LZD, and PAS were administered individually to the patient. The dose manipulation for CFZ is done as per Table 4 according to the prescribed dose for the patient. It is difficult to predict if all the liquid is squeezed into the child's mouth as the capsule is a shade of dark brown and its contents cannot be viewed. The liquid present inside is thick and greasy.

For the administration of INH, LFX, TRD, folic acid, and pyridoxine, required doses were withdrawn via syringe from the manipulated volume as per Table 4, and added to a single medicine cup. Ferrous and multivitamin syrup doses were also added to the measuring cup for a single administration to the patient. As the ferrous supplement and the multivitamin are formulated as syrups for oral consumption, these were added to try and mask the taste of the added tablets and capsules, which could be unpalatable. This resulted in a significant volume of liquid to be administered to the patient.

Manipulations for the 7 drugs observed were done in accordance with guidelines [3, 22–24]. The method of administration for CFZ is not recommended in any package insert or guideline, but that this was considered the most practical method in this setting.

Discussion

Several studies have been conducted previously that detail the challenging DR-TB journey for children and their caregivers due to the many obstacles that impact diagnosis and management [12, 16, 17, 25]. Historically, DR-TB treatment for children involved treatment with medication with significant adverse drug reactions [14, 26–29]. Recent advancements, such as the introduction of new and repurposed drugs, shorter regimens, improved formulations, and injectable-free, all-oral regimens, offer promise [30, 31]. However, the widespread availability of these innovations, particularly for children, remains limited in many countries [16].

There has been a gradual expansion in the availability of child-friendly formulations of second-line TB drugs in the last few years [8, 32]. The Stop TB Partnership's GDF, renowned as the largest global provider of quality-assured TB drugs, has taken steps to integrate child-friendly formulations for various medications, including bedaquiline, clofazimine, cycloserine/terizidone, ethambutol, ethionamide, levofloxacin, moxifloxacin, and pyrazinamide, into their product offerings [8, 32]. Furthermore, in partnership with the Sentinel Project, they have been facilitating the global adoption of these formulations. Although some countries have yet to approve these formulations, rendering them inaccessible (e.g., the European Union and SA), those with access should prioritize their procurement [33]. At the time that the study was conducted, there were no child-friendly formulations except for LZD that were available at the study site and manipulations were done in accordance with guidelines published with the exception of CFZ.

The administration of solid dosage forms manipulated for the treatment of DR-TB in children can be time-consuming, challenging, and non-adherence is a major cause of treatment failure [34]. Multiple factors may contribute to this issue, including the absence of paediatric formulations, high pill burden, poor palatability, extended therapy duration, and medication toxicity [35]. The main reasons for the manipulation of solid dosage forms in this study were the lack of suitable dosage forms and the

Table 4 Drug administration in the paediatric ward

Drug	Formulation	Type of Manipulation	Dose manipulations observed
Bedaquiline	100 mg uncoated tablet	Tablet dispersed in distilled water.	Dispersed one tablet (100 mg) in a a standard volume of distilled water (10mls) and the required volume administered. Administered on its own (not mixed with other preparations).
Clofazimine	100 mg gel capsule	Capsule is cut	The tip of the capsule is cut. The liquid in the capsule is squeezed directly into the child's mouth. OR A needle is inserted into the capsule to withdraw the liquid, which is then administered to the child via the syringe. Administered on its own (not mixed with other preparations).
Delamanid	50 mg film coated tablet	Tablet dispersed in distilled water.	Dispersed one tablet (50 mg) in a standard volume of distilled water (10mls) and the required volume administered. If the dose is 50 mg, draw 10 ml to administer to the child. Calculation: 50 mg – 10mls = 50 mg – x = 10mls Administered on its own (not mixed with other preparations).
Isoniazid	300 mg scored tablet	The tablet is cut/broken in half and dispersed in distilled water.	One tablet (300 mg) is broken in half. The half tablet (150 mg) is dispersed in a standard volume of distilled water (10mls). The prepared dose is withdrawn and added to the medicine cup to be mixed with the other doses for administration.
Levofloxacin	250 mg film coated tablet	The tablet is dispersed in distilled water. The dose is calculated and then the required proportion of liquid is administered.	Dispersed one tablet (250 mg) in a standard volume of distilled water (10mls) and the required volume administered. E.g., Dose prescribed is 150 mg once daily. Calculation: 250 mg – 10mls = 150 mg – x = 6mls required for administration The calculated dose is drawn into a syringe and added to the medicine cup to be mixed with the other doses for administration. The remaining dose is discarded.
Linezolid	20 mg/ml suspension	No manipulation is required. Suspension is reconstituted.	
Terizidone	250 mg capsule	Capsule contents are opened and dissolved in distilled water. The dose is calculated and then the required proportion of liquid is administered.	Open and dissolve the contents of one capsule (250 mg) in a standard volume of water (10mls). Sufficient time is allowed for the capsule contents to dissolve (around 30 min). E.g., Dose prescribed is 175 mg once daily. Calculation: 250 mg – 10mls = 175 mg – x x = 7mls The calculated dose is drawn into a syringe and added to the medicine cup to be mixed with the other doses for administration. The remaining dose is discarded.
P-aminosalicylic acid	4 g sachet	Mixed in a yoghurt.	Available as granules that are mixed in yoghurt and administered to the patient before food at 6 am.

Calculations of the dose are guided by the formula: Dose available = Prescribed dose / x. Each tablet was considered to be equivalent to 10mls

lack of strength suitable for paediatric patients for DR-TB that were available. Manipulation of solid dosage forms for administration can be complicated and therefore open to errors and the possibility of incorrect dosing. Few guidelines exist and support dose manipulations of solid dosage forms for paediatric administration based on scientific research. Although dose manipulations for paediatrics may be common practice for many disease conditions, these manipulations are done according to practice and not scientific research. Studies should be conducted to determine if the bioavailability remains the same when the dosage form is manipulated for all second-line drug treatment to ensure patient safety and optimum treatment outcomes.

During the observation of nurses preparing the manipulated doses, time played a major role as the task was relatively long given the many drugs prescribed for DR-TB. In some instances, the tablets had to be broken in half which can often result in the damaging the entire tablet. The capsules had to be opened. The distilled water needed to be measured and each tablet or capsule dispersed individually. Once each dose had been prepared,

the required dose was then withdrawn and added to a single medicine cup. There was a large volume of liquid that needed to be administered to the child. The flavour and colour of the liquid seemed to affect the tolerability of the child as they would often reject the medicine by spitting it out or crying. Although the nurses had developed strategies to ensure that the children consume all the medicine, the process is difficult on both the child and the nurse. Previous studies have detailed the physical and emotional trauma that nurses, children and caregivers go through in this process. Nurses have even complained about the cumbersome and inconvenient process of preparation and administration of these manipulated doses to the children.

The findings of the study emphasize the urgent need for child-friendly formulations to be made available for all second-line drugs. Children afflicted with DR-TB constitute a vulnerable demographic, often lagging behind in accessing advancements in paediatric care and specifically in DR-TB management. Furthermore, focus should be towards locating undiagnosed cases of TB in children, ensuring they receive suitable treatment, and establishing a stronger evidence base to advocate for all consistent supply of formulations that are child-friendly for all second-line drugs that is available globally.

To our knowledge, this is the first study to report the current practices in dosage form manipulations for paediatric DR-TB treatment. The study was conducted facing some limitations. The observation was done in one hospital and one ward therefore the results are not representative of the population. At the time of data collection, only two patients (less than 2 years of age) were admitted, therefore observation was limited. Additionally, the observations did not include administration and manipulation by caregivers. The above findings present the situation about DR-TB at the time the study was conducted and may not be a permanent feature at the study site and throughout the country.

Conclusion

There is an increasing number of children worldwide needing treatment for DR-TB. Paediatric DR-TB patients have traditionally been treated with off-label adult pharmaceuticals or extemporaneous compounding, which is not ideal for paediatric patients due to a lack of product safety, efficacy, and evidence-based guidelines. [35] Furthermore, there are limited formulations suitable for children that are widely available. This has resulted in the manipulation of existing formulations to liquid preparations, either by dissolving tablets or opening capsules, to administer to paediatric patients. Establishing the correct dose and our ability to administer it to the child successfully are equally important. We need to encourage and work with manufacturers to adapt medicines to the needs of children but should also ensure that pharmacists and carers have information to adapt dosage forms safely and to extemporaneously formulate if necessary. Although there has been development of child-friendly dosage forms in recent years these drugs lack availability and registration in many countries. The healthcare sector needs to focus on identifying cases of children with DR-TB to build evidence to advocate for registration of child-friendly dosage forms thereby ensuring a sustainable supply of medication.

Acknowledgements
The authors would like to thank the nursing staff for the opportunity to observe manipulations of dosage forms in clinical practice.

Author contributions
S.H., V.B., and F.O. conceived the study design. S.H. obtained the data from the study site.S.H. performed the analysis of the data. S.H. wrote the draft of the manuscript with V.B. and F.O. assisting with further drafts and revisions. All authors reviewed and approved the final version of the manuscript.

Funding
This research received no funding.

Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and permission to use the data was obtained from the Gauteng Department of Health and Sizwe Tropical Diseases Hospital. Informed consent was signed by all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
None.

Competing interests
The authors declare no competing interests.

Disclaimer
The findings and conclusions in this manuscript are those of the authors and do not necessarily represent Sizwe Tropical Diseases Hospital or South Africa.

Author details
[1]School of Health Sciences, University of Kwazulu-Natal, Westville Campus, Private Bag X54001, Durban 4000, South Africa

Received: 6 December 2023 / Accepted: 30 July 2024
Published online: 12 August 2024

References

1. Global Tuberculosis Report. 2023. World Health Organization. https://www.who.int/teams/global-tuberculosis-programme/tb-reports, Accessed: 29 April 2024.
2. Clinical Management of Rifampicin-Resistant Tuberculosis. Updated clinical reference guide. National Department of Health. South Africa; September 2023. pp. 6–7.
3. WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. WHO; 2022.

4. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modeling study. Lancet Infect Dis. 2016;16:1193–201.
5. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, Pagano M, Becerra MC, Cohen T. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383:1572–9.
6. Overcoming the drug. -resistant TB crisis in children and adolescents. World Health Organization; November 2020.
7. Reuter A, Hughes J, Furin J. Challenges and controversies in childhood tuberculosis. Lancet. 2019;294:967–78.
8. Stop TB. Partnership—Medicine catalog Global Drug Facility. Global Drug Facility; 2021.
9. Skwierczynski C, Conroy S. How long does it take to administer oral medicines to children? Pediatr Perinat Drug Therapy. 2008;8:145–9.
10. Conroy S, Sweis D, Planner C, Yeung V, Collier J, Haines L, Wong IC. Interventions to reduce dosing errors in children: a systematic review of the literature. Drug Saf. 2007;30(12):1111–25.
11. Chiang SS, Roche S, Contreras C, Alarcón V, Del Castillo H, Becerra MC, Lecca L. Barriers to the diagnosis of childhood tuberculosis: a qualitative study. Int J Tuberculosis Lung Disease. 2015;19(10):1144–52.
12. Furin J, Mafukidze A, Brigden G, du Cros P, Golin R, Harausz E, Seddon JA, Ustero P, Garcia-Prats AJ. A bitter pill to swallow: the need for better medications for drug-resistant tuberculosis in children. Int J Tuberculosis Lung Disease. 2015;19(Suppl 1):55–60.
13. Donald PR. The assessment of new anti-tuberculosis drugs for a paediatric indication. Int J Tuberculosis Lung Disease. 2007;11(11):1162–5.
14. Taneja R, Garcia-Prats AJ, Furin J, Maheshwari HK. Paediatric formulations of second-line anti-tuberculosis medications: challenges and considerations. Int J Tuberculosis Lung Disease. 2015;19(Suppl 1):61–8.
15. Schaaf HS, Moll AP, Dheda K. Multidrug- and extensively drug-resistant tuberculosis in Africa and South America: epidemiology, diagnosis and management in adults and children. Clin Chest Med. 2009;30:667–83.
16. Wademan DT, Viljoen L, Jacobs S, Meyerson K, Nombewu Y, Busakwe L, Schaaf HS, Hesseling AC, Winckler J, Garcia-Prats AJ, Hoddinott G. Children´s priorities to improve the acceptability of MDR-TB treatment: qualitative data from South Africa. Int J Tuberculosis Lung Disease. 2023;27(7):543–50.
17. Misra S, Misra N, Seepamore B, Holloway K, Singh N, Ngozo J, Dlamini V, Radebe Z, Ndjeka NO, Furin J. 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;17(9):e0274741.
18. Du Preez K, Seddon JA, Schaaf HS, Hessling AC. Where are we in the battle of ending tuberculosis in children and adolescents in South Africa? South Afr Med J. 2020;110(5):345–6.
19. Misra N. We are the Children… hear our voices: improving Access to Child-Friendly formulations of Drug Resistant Tuberculosis Medicine: the KwaZulu-Natal experience. South African Pharmaceutical Journal. 90, 6. Pages 56–8.
20. Richey RH, Craig JV, Shah UU, Nunn AJ, Turner MA, Barker CE, Ford JL, Peak M. MODRIC - manipulation of drugs in children. Int J Pharm. 2013;457(1):339–41.
21. Zahn J, Hoerning A, Trollmann R, Rascher W, Neubert A. Manipulation of Medicinal products for oral administration to paediatric patients at a German University Hospital: an observational study. Pharmaceutics. 2020;12(6):583.
22. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO; 2022.
23. The Sentinel Project for Pediatric Drug-Resistant Tuberculosis and Stop TB Partnership Global Drug Facility. Drug sheets for dispersible formulations. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; February; 2019.
24. Schaaf HS, Hughes J. Current treatment of drug-resistant tuberculosis in children. Indian J Pediatr. 2023 Nov 23.
25. Das M, Mathur T, Ravi S, Meneguim AC, Iyer A, Mansoor H, Kalon S, Hossain FN, Acharya S, Ferlazzo G, Isaakidis P, Thakur HP. Challenging drug-resistant TB treatment journey for children, adolescents and their care-givers: a qualitative study. PLoS ONE. 2021;16(3):e0248408.
26. Garcia-Prats AJ, Schaaf HS, Draper HR, Garcia-Cremades M, Winckler J, Wiesner L, Hesseling AC, Savic RM. Pharmacokinetics, optimal dosing, and safety of linezolid in children with multidrug-resistant tuberculosis: combined data from two prospective observational studies. PLoS Med. 2019;16(4):e1002789.
27. Zimri K, Casper R, Hoddinott G, Schaaf HS, Garcia-Prats AJ, Rose PC, Hesseling AC, Viljoen L. A novel approach for eliciting adolescent MDR-TB treatment tolerability: qualitative data from South Africa. Int J Tuberculosis Lung Disease. 2020;24(1):43–7.
28. Akkerman O, Aleksa A, Alffenaar JW, Al-Marzouqi NH, Arias-Guillén M, Belilovski E, Bernal E, Boeree MJ, Borisov SE, Bruchfeld J, Cadiñanos Loidi J, Cai Q, Caminero JA, Cebrian Gallardo JJ, Centis R, Codecasa LR, D'Ambrosio L, Dalcolmo M, Danila E, Dara M, Davidavičienė E, Davies Forsman L, De Los Rios Jefe J, Denholm J, Duarte R, Elamin SE, Ferrarese M, Filippov A, Ganatra S, Garcia A, García-García JM, Gayoso R, Giraldo Montoya AM, Gomez Rosso RG, Gualano G, Hoefsloot W, Ilievska-Poposka B, Jonsson J, Khimova E, Kuksa L, Kunst H, Laniado-Laborín R, Li Y, Magis-Escurra C, Manfrin V, Manga S, Marchese V, Martínez Robles E, Maryandyshev A, Matteelli A, Migliori GB, Mullerpattan JB, Munoz-Torrico M, Mustafa Hamdan H, Nieto Marcos M, Noordin NM, Palmero DJ, Palmieri F, Payen MC, Piubello A, Pontali E, Pontarelli A, Quirós S, Rendon A, Skrahina A, Šmite A, Solovic I, Sotgiu G, Souleymane MB, Spanevello A, Stošić M, Tadolini M, Tiberi S, Udwadia ZF, van den Boom M, Vescovo M, Viggiani P, Visca D, Zhurkin D, Zignol M. Members of the International Study Group on new anti-tuberculosis drugs and adverse events monitoring. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: a global feasibility study. Int J Infect Disease. 2019;83:72–6.
29. Borisov S, Danila E, Maryandyshev A, Dalcolmo M, Miliauskas S, Kuksa L, Manga S, Skrahina A, Diktanas S, Codecasa LR, Aleksa A, Bruchfeld J, Koleva A, Piubello A, Udwadia ZF, Akkerman OW, Belilovski E, Bernal E, Boeree MJ, Cadiñanos Loidi J, Cai Q, Cebrian Gallardo JJ, Dara M, Davidavičienė E, Forsman LD, De Los Rios J, Denholm J, Drakšienė J, Duarte R, Elamin SE, Escobar Salinas N, Ferrarese M, Filippov A, Garcia A, García-García JM, Gaudiesiute I, Gavazova B, Gayoso R, Gomez Rosso R, Gruslys V, Gualano G, Hoefsloot W, Jonsson J, Khimova E, Kunst H, Laniado-Laborín R, Li Y, Magis-Escurra C, Manfrin V, Marchese V, Martínez Robles E, Matteelli A, Mazza-Stalder J, Moschos C, Muñoz-Torrico M, Mustafa Hamdan H, Nakčerienė B, Nicod L, Nieto Marcos M, Palmero DJ, Palmieri F, Papavasileiou A, Payen MC, Pontarelli A, Quirós S, Rendon A, Saderi L, Šmite A, Solovic I, Souleymane MB, Tadolini M, van den Boom M, Vescovo M, Viggiani P, Yedilbayev A, Zablockis R, Zhurkin D, Zignol M, Visca D, Spanevello A, Caminero JA, Alffenaar JW, Tiberi S, Centis R, D'Ambrosio L, Pontali E, Sotgiu G, Migliori GB. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. Eur Respir J. 2019;54(6):1901522.
30. Purchase SE, Garcia-Prats AJ, De Koker P, Draper HR, Osman M, Seddon JA, Schaaf HS, Hesseling AC. Acceptability of a Novel Levofloxacin Dispersible Tablet Formulation in Young Children exposed to Multidrug-resistant tuberculosis. Pediatr Infect Dis J. 2019;38(6):608–10.
31. Winckler JL, Draper HR, Schaaf HS, van der Laan LE, Hesseling AC, Garcia-Prats AJ. Acceptability of levofloxacin, moxifloxacin and linezolid among children and adolescents treated for TB. Int J Tuberculosis Lung Disease. 2020;24(12):1316–8.
32. StopTB/GDF's Paediatric Drug-Resistant TB (DR-TB) Donation Initiative. 2021. http://sentinel-project.org/2019/02/18/stoptbgdfs-paediatric-drug-resistant-tb-dr-tb-donation-initiative/ Accessed on: 22 April 2023.
33. Howell P, Achar J, Huang GKL, Mariandyshev A, Schaaf HS, Garcia-Prats AJ. Treatment of rifampicin-resistant tuberculosis disease and infection in children: Key updates, challenges and opportunities. Pathogens. 2022;11(4):381. https://doi.org/10.3390/pathogens11040381.
34. Piñeiro Pérez R, Santiago García B, Fernández Llamazares CM, Baquero Artigao F, Noguera Julian A, Mellado Peña MJ. The challenge of administering antituberculosis treatment in infants and pre-school children. pTBred Magistral Project] Anales de Pediatria (Barcelona). 2016;85(1):4–12. en representación de pTBred (Red Española de Estudio de Tuberculosis Pediátrica).
35. 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. Eur Respir J. 2021;58(3):2101196.

Publisher's Note