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Acceptability of levofloxacin, moxifloxacin and linezolid among children and adolescents treated for TB

J. L. Winckler, **H. R. Draper**, **H. S. Schaaf**, **L. E. van der Laan**, **A. C. Hesseling**, **A. J. Garcia-Prats**

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

Dear Editor,

Globally, there are an estimated 32 000 incident cases of rifampicin-resistant TB (RR-TB) in children each year.[1] The treatment of RR-TB requires multi-drug regimens with second-line anti-TB medication used for at least 9 months. Child-friendly second-line anti-TB medication formulations that are palatable and easily administered are not widely available. Therefore, solid tablets designed for adults must be manipulated through crushing or splitting and mixing with water to administer to young children, which may affect the medication's acceptability. Acceptability is defined as the overall suitability of a formulation, including the dose volume or size and palatability. Palatability is the overall acceptance of taste, smell, volume or size, and texture of an oral medication, and is an important determinant of medication acceptability in children.[2] Although anecdotally many second-line anti-TB medications are poorly acceptable (especially when crushed) there is limited published research on children. Children may have different perceptions relative to adults, therefore it is important to complete assessments in children.[2] A formulation's acceptability may impact on treatment adherence, a critical factor in treatment success.[3]

The objective of this study was to characterise the acceptability in children of key second-line TB medications levofloxacin (LVX), moxifloxacin (MFX) and linezolid (LZD), routinely used for RR-TB. This was a nested cross sectional study within a larger observational pharmacokinetic study (MDRPK2, NIH R01HD083047) in Cape Town, South Africa. MDRPK2 enrolled children < 18 years of age routinely treated for RR-TB for pharmacokinetic sampling of LVX, MFX and LZD.[4] The acceptability of routinely administered formulations was assessed in a convenience sample of participants enrolled in the main study.

Children were treated with 5–7 drug regimens consistent with local and national recommendations, with medications available through the local TB programme.[5] LZD was administered as 600 mg tablets swallowed whole or as a 20 mg/mL paediatric suspension (Pfizer, San Juan, Puerto Rico). LVX (Sandoz, Ljubljana, Slovenia and Austell, Mumbai, India) was administered as 250 mg tablets swallowed whole or crushed with water. MFX

janawinckler@sun.ac.za.

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400 mg tablets (Dr Reddy's Laboratories, Hyderabad, India) were swallowed whole or given as a 20 mg/mL extemporaneous suspension prepared using the 400 mg tablets according to a published method with demonstrated stability.[6]

Acceptability assessments were made after a dose administered by the study team at a pharmacokinetic sampling visit 2–8 weeks after starting RR-TB treatment. A standard questionnaire was used, consisting of a self-reported component soliciting ranked responses from older children able to self-report (generally children ≥ 5 years of age), and an observed component soliciting ranked responses by the study personnel observing younger children, who were unable to self-report. For older, self-reporting children, the taste, smell, look and texture were ranked using a five-point facial hedonic scale (dislike very much, dislike, neutral, like and like very much). Size and amount of drugs were rated simultaneously on a three-point scale (size/volume okay, size/volume too large and size/volume much too large). For young children unable to self-report, the study team observed their intake and documented the amount swallowed and the child's reaction to the volume of drug using a ranked five-point and three-point scale, respectively. The child's apparent reaction to the taste of the dose was assessed using a five-point facial hedonic scale. The five-point scale cut-offs for taste (self-reported and observed), look (self-reported only), smell (self-reported only) and texture (self-reported only) were collapsed to form binary variables (dislike very much/dislike versus neutral/like/like very much). For both self-reported and observed assessments, the amount of drug was dichotomised: the amount or volume was large or much too large, versus the amount or volume was okay. For the observed assessments, the amount swallowed was dichotomized: everything swallowed vs. everything not swallowed (small runlet/spat out/choked on/refused). All analyses were conducted using Stata v15.0 Special Edition (StataCorp, College Station, TX, USA).

Twenty-six children were enrolled. The median age was 6.9 years (IQR 4.1–12.6), 12 (46%) were male, and 2 (8%) were HIV-infected. Observed assessments were completed by study personnel in 11 young children (median age 3.7 years, IQR 1.8–4.3), while 15 older children provided self-reported assessments (median age 12.0 years, IQR 7.8–12.9). The Table summarizes the results by medication, formulation and assessment type.

Crushed tablets of LVX and MFX had poor acceptability among children being treated for RR-TB. Anecdotally, the fluoroquinolones are reported to be bitter to taste, even to adults, especially when crushed or formulated into a suspension. We have previously shown that a taste-masked dispersible tablet of LVX was more acceptable to children and caregivers than the crushed adult tablet.[7] Our data on LVX are consistent and confirms the poor acceptability of currently available crushed LVX tablets. An extemporaneous suspension made from MFX tablets had similarly poor acceptability in our study, even with the use of a sweetened suspending agent. Poor medication acceptability is an important challenge for patients and caregivers, with a potential negative impact on families' experience of treatment, which may reduce long-term adherence.[3,8,9] LVX and MFX dispersible tablet formulations have been recently developed and are available for procurement from the Global Drug Facility.[10] Administration of crushed adult tablet formulations to young children may be more convenient for TB programmes, minimising cost and simplifying ordering and storage of medication, but is not an acceptable strategy for paediatric treatment.

Countries must prioritize procurement and administration of these more child-friendly formulations for children with RR-TB. In addition, poor palatability of whole tablets was reported in adolescents in our study, who are more likely to also reflect adults' experience of taking RR-TB medications. Patient-friendly TB medication is needed for all individuals treated for RR-TB.

The LZD tablet was also disliked or disliked very much by the majority of participants. Although the LZD suspension was acceptable in the majority of children in our study, it is expensive and not widely available. Suspensions are not ideal formulations, and there is clear consensus that solid oral dosage formulations are preferred.[11] LZD, newly classified as a Group A priority medication for RR-TB treatment by the WHO, is likely to be used more frequently in future.[4] A child-friendly, high-quality dispersible LZD formulation, available at a reasonable cost, is therefore urgently needed.

A limitation of this study is its modest sample size. Additionally, acceptability assessments were completed during pharmacokinetic sampling days, which can be stressful to children and may therefore have affected our results. The lack of a validated method for assessing acceptability, especially in young children, remains a challenge. Few young children in this convenience sample received LVX, even though it is the preferred fluoroquinolone in this age group. However, we have previously reported on LVX acceptability in this age group.[7]

Despite these limitations, our study contributes valuable objective data for what has until now primarily been anecdotal experience. The most widely available formulations of these important second-line TB drugs have poor acceptability in children with RR-TB. Affordable, high-quality child-friendly formulations are essential for the acceptable treatment of RR-TB in children across the age spectrum.

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References

1. Jenkins HE, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014; 383: 1572–1579. [PubMed: 24671080]
2. Mennella JA, Beauchamp GK. Optimizing oral medications for children. Clin Ther 2008; 30: 2120–2132. [PubMed: 19108800]
3. Baguley D, Lim E, Bevan A, Pallet A, Faust SN. Prescribing for children—taste and palatability affect adherence to antibiotics: R a review. Arch Dis Child 2012; 97: 293–297. [PubMed: 22088684]
4. World Health Organization. WHO consolidated guidelines on the treatment of drug-resistant tuberculosis, 2019. Geneva, Switzerland: WHO, 2019. https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1. Accessed December 2019.
5. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. Geneva, Switzerland: WHO, 2016. https://apps.who.int/medicinedocs/documents/s23097en/s23097en.pdf. Accessed Decmeber 2019.

6. Hutchinson DJ, Johnson CE, Klein KC. Stability of extemporaneously prepared moxifloxacin oral suspensions. Am J Health Syst Pharm 2009; 66: 665–667. [PubMed: 19299374]

7. Purchase SE, et al. Acceptability of a novel levofloxacin dispersible tablet formulation in young children exposed to multidrug-resistant tuberculosis. Pediatr Infect Dis J 2019; 38: 608–610. [PubMed: 30550511]

8. Wademan DT, et al. Acceptability of a first-line antituberculosis formulation for children: qualitative data from the SHINE trial. Int J Tuberc Lung Dis 2019; 23: 1263–1268. [PubMed: 31931909]

9. Bryson SP. Patient-centred, administration friendly medicines for children—an evaluation of children's preferences and how they impact medication adherence. Int J Pharm 2014; 469: 257–259. [PubMed: 24797763]

10. StopTB Partnership. Global Drug Facility Product Catalog 2020. Geneva, Switzerland: StopTB Partnership, http://www.stoptb.org/gdf/drugsupply/product_catalog.asp. Accessed April 2020.

11. Orubu ES, Tuleu C. Medicines for children: flexible solid oral formulations. Bull World Health Organ 2017; 95: 238–240. [PubMed: 28250539]

Table

Assessments of levofloxacin, moxifloxacin and linezolid acceptability by formulation type among children treated for rifampicin-resistant TB

	Levofloxacin		Moxifloxacin		Linezolid	
	Crushed solid tablet in water (*n* = 3) *n* (%)	**Solid tablet swallowed whole (*n* = 9) *n* (%)**	**Extemporaneous Suspension (*n* = 10) *n* (%)**	**Solid tablet swallowed whole (*n* = 4) *n* (%)**	**Suspension (*n* = 6) *n* (%)**	**Solid tablet swallowed whole (*n* = 6) *n* (%)**
Self-reported assessment						
Child disliked or disliked very much the taste of the formulation	3 (100)	3 (33)	9 (90)	1 (25)	3 (50)	4 (67)
Child disliked or disliked very much the look of the formulation	2 (67)	2 (22)	8 (80)	0	2 (33)	4 (67)
Child disliked or disliked very much the smell of the formulation	2 (67)	2 (22)	9 (90)	0	2 (33)	3 (50)
Child disliked or disliked very much the texture of the formulation	3 (100)	3 (33)	9 (90)	1 (25)	3 (50)	4 (67)
Child felt the amount/volume was too large or much too large	2 (67)	4 (44)	7 (70)	2 (50)	2 (33)	0
Volume of dose, mL, median [IQR]	10 [8–10]	—	15 [10–20]	—	10 [8–10]	—
Children receiving more than 1 tablet per dose	—	8 (89)	—	1 (25)	—	0
Observed assessment						
Everything swallowed, no liquid residuals found	—	—	8 (89)	—	8 (100)	—
Child appeared to dislike or dislike very much the taste	—	—	7 (78)	—	2 (25)	—
Child appeared to feel the volume was large or much too large	—	—	6 (67)	—	1 (13)	—