"We are the Children…. Hear our Voices": Improving Access to Child-Friendly Formulations of Drug Resistant Tuberculosis Medicine: The KwaZulu-Natal Experience

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Background

The past five years have seen revolutionary changes in the diagnosis and management of rifampicin-resistant tuberculosis (RR-TB), including the use of new and repurposed drugs and novel therapeutic approaches.[1] Following years of stagnation in the drug development pipeline, the introduction of two new agents, bedaquiline and delaminid, and the use of the repurposed medicines, clofazimine and linezolid, have provided hope for patients globally, reducing the pill burden and duration of treatment.[2] Critically, this has also enabled all-oral regimens, avoiding the adverse events associated with aminoglycosides and the need for in-hospital treatment.

Based on new evidence of safety and efficacy of the new and repurposed medicines emanating from research studies conducted globally, with South Africa (SA) being a major contributor, the World Health Organization (WHO) issued a "Rapid Communication" on 17 August 2018.[3] The WHO communication included radically altered recommendations for the treatment of drug-resistant tuberculosis. These recommendations were made based on an individual patient data meta-analysis of more than 12,000 adults and programmatic data from more than 50 countries and data from phase II and III randomised controlled trials. For the first time ever, WHO was recommending all-oral treatment regimens for the majority of individuals with drug resistant TB (DR-TB) and revised the priority "groupings" of individual medications that should be used for regimen design (Figure 1). The new and repurposed medicines were now included as core medicine in the treatment regimen.

Group	Medicine	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Goup A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Imp-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

[1] Evidence of the safety and effectiveness of Bdq beyond 6 months was insufficient for review; extended Bdq use in individual patients will need to follow 'off-label' use best practice

[2] Optimal duration of use of Lzd is not established. Use for at least 6 months was shown to be highly effective, although toxicity may limit use.

Figure 1: Grouping of medicine recommended for use in longer MDR TB regimens

Source: WHO Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)[3]

The gap

Although the analyses and recommendations were largely focused on adults as only a small number of children are diagnosed and treated for DR-TB each year, and thus the evidence base in children is not as robust as that for adults, the new WHO recommendations for regimen design also apply to the treatment of paediatric DR-TB. It was recommended that regimen construction for children should prioritise *Group A and B medications,* where possible. Children should be offered regimens containing medications that have been shown to be associated with improved outcomes and a lower risk of mortality in adults, including bedaquiline, linezolid, clofazimine and the later-generation fluoroquinolones.[4]

SA as a global leader in introducing innovation to the field of DR-TB rapidly adopted the WHO recommendations into their policy guidelines.[2–7] The announcement by the National Department of Health of the adoption of the injectable-free regimen in patients 12 years and older, with bedaquiline replacing kanamycin, an injectable agent that cause nephron- and ototoxicity (irreversible) in many patients[8], was applauded by activists and healthcare workers. However, many raised concerns that children's needs were not being met due to the absence of child friendly formulations of second line DR-TB medicine.[9-11] Whilst children represent a substantial proportion of persons with TB disease, with an estimated 30,000 children becoming sick with multidrug resistant tuberculosis (MDR-TB) globally each year, they lack the same access to diagnosis and treatment as their adult counterparts.

In the SA public sector, medicine is generally procured on the basis of transversal tenders. A review of the tuberculosis tender confirmed that only adult formulations of second-line DR-TB medicine, with limited availability of linezolid suspension, had been awarded. It was noted that children were treated with adult formulations that had to be cut, crushed and mixed. This may result in incorrect dosing, prolonged hospitalisation, and significant staff time for preparing and delivering medications. This was the accepted standard for many years as there were no alternatives.

The opportunity

In 2017, dispersible child-friendly formulations of DR-TB medicine became available on the global market. The Global Drug Facility (GDF), in collaboration with Sentinel Project on Pediatric Drug-Resistant Tuberculosis, proposed a global pooled procurement strategy with all countries contributing to the demand. GDF donated an initial supply to countries with the aim of encouraging countries to gain programmatic experience with these medications, and to facilitate the global roll-out of these products. These novel new formulations were scored to ensure consistency in dosing, dispersible to dissolve easily in water, with smaller sizes for more precise dosing and easier administration and were quality assured. Their availability meant that using adult tablets that had to be manipulated could no longer be justified. These were not new drugs, but different formulations of existing drugs to make treating children with DR-TB easier, safer and more tolerable.

The journey

Optimal stakeholder engagement was needed to improve access to the child-friendly formulations. The new formulations were not registered in SA and an application had to be made to the South African Health Products Regulatory Authority (SAHPRA), to obtain permission to use an unregistered product in the country.[12] Representation was made to the National Department of Health Affordable Medicines Directorate to motivate for the need for the child friendly formulations, requesting support to accept the donation as per policy guidelines.[13] The need for the child-friendly formulations and products available for donation from GDF was also supported by the KwaZulu-Natal (KZN) Provincial Pharmaceutical and Therapeutics Committee. Quantification and forecasting were done for each product available from GDF, based on the past 3 years' case registrations of children under 10 years in KZN and the current DR-TB treatment guidelines. A need for ethambutol 100mg, pyrazinamide 150mg, levofloxacin 100mg and clofazimine 50mg dispersible tablets was identified. A submission to accept the donation of child-friendly formulations was drafted from the KZN Head of Pharmaceutical Services and HIV and AIDS/STI/TB (HAST) Manager to the KZN Head of Health, which was approved. A grant agreement between GDF and KZN was signed and a procurement request form was signed by the HAST Manager. Equity Pharmaceuticals was approached to facilitate clearing and forwarding of the medicine from the airport to King Dinuzulu Hospital Complex (KDHC). In 2020, KZN received dispersible tablets of ethambutol100mg, pyrazinamide 150mg and levofloxacin. In 2021, dispersible clofazimine 50mg was received.

Standard operating procedures (SOPs) for the pharmacist, nurse and doctor were developed based on actual experience. Training of end users and caregivers regarding the products and regulatory requirements such as informed consent forms to be completed prior to initiation and six-monthly progress reports that monitored outcomes and adverse events. A total of 24 children benefited from the access to the child-friendly formulations.

Lessons learnt

The KZN experience has shown that convincing the regulatory bodies to approve the use of child-friendly formulations in the absence of robust evidence in children is challenging, but possible. Lack of evidence of safety and efficacy in children hinders inclusion into the NDoH's Standard Treatment Guidelines (STGs) and Essential Medicines List (EMLs). Children, caregivers, nurses and clinicians reported good adherence, ease of administration and better dosing with child-friendly formulations.

Way forward

The KZN experience has changed the narrative from lack of child-friendly formulations to **"Where are the Children?"**. The focus has to move to finding the missing cases of children, placing them on appropriate treatment and building the evidence base to lobby for a sustainable supply of child-friendly formulations.

References

1. Gandhi NR, Brust JCM, Sarita Shah N. A new era for treatment of drug-resistant tuberculosis. European Respiratory Journal 2018; 52: 1801350.
2. World Health Organization. Consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization, Geneva, 2019.
3. World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). World Health Organization, Geneva, 2018.
4. Harausz EP, Garcia-Prats AJ, Seddon JA, Schaaf HS *et al*.; New and repurposed drugs for pediatric multidrug-resistant tuberculosis practice-based recommendations; Am J Respir Crit Care Med 2017; 195 (10): 1300–1310.
5. Ndjeka N, Hughes J, Reuter A, Conradie F, Enwerem M, Ferreira H, *et al*. Implementing novel regimens for drug-resistant TB in South Africa: what can the world learn? Int J Tuberc Lung Dis 2020; 24(10): 1073-1080.
6. Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, *et al*. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. European Respiratory Journal 2018; 52: 1801528.
7. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, *et al*. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018; 6: 699–706.
8. National Department of Health. Interim clinical guidance for implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children. National Department of Health, Pretoria, 2018.
9. Zali M. Activist concerned about lack of TB medication for children. Health-e News, 4 December 2019.
10. Seddon JA, Schaaf HS, Marais BJ, McKenna L, Garcia-Prats AJ, Hesseling AC, *et al*. Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis. Lancet Respir Med. 2018; 6(9): 662-664.
11. Schaaf, HS, Garcia-Prats, AJ, McKenna, L, Seddon, JA. Challenges of using new and repurposed drugs for the treatment of multidrug-resistant tuberculosis in children. Expert Rev Clin Pharmacol 2018;11(3): 233-244.
12. South African Health Products Regulatory Authority. Guideline for Section 21 access to unregistered medicines (SAHPGL-CEM-S21-02), 5 August 2022. Accessible at https://www.sahpra.org.za/wp-content/uploads/2022/01/SAHPGL-CEM-S21-02_v4-Guideline-for-Section-21-Access-to-Unregistered-Medicines.pdf
13. South African Health Products Regulatory Authority. Donation of medicines, medical devices and IVDs (5.08), 16 April 2020. Accessible at https://www.sahpra.org.za/wp-content/uploads/2021/05/Revised-Guideline-DONATION-OF-MEDICINES-MEDICAL-DEVICES-AND-IVDs.pdf