Paediatric formulations for the treatment of drug resistant TB

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EDITORIAL

Paediatric formulations for the treatment of drug resistant TB: closing the gaps

The United Nations High-Level Meeting on TB set clear targets for the treatment of drug-susceptible and drug-resistant TB (DR-TB) in children over an initial 5-year period (2018–2022). The target for TB treatment provided to children (<15 years of age) is less than 50% fulfilled, reaching only 1.4 of the 3.5 million children targeted (41%). The situation is even worse for children with rifampicin- and multidrug-resistant TB (MDR-TB), with only 11% of the target reached (12,000 out of the 115,000).[1] Although treatment success is high in children able to access TB treatment (88% in 2019), most child TB cases miss out on effective treatment. In fact, it is estimated that more than 90% of TB deaths in children occur in those unable to access effective treatment and care, and TB is now recognised as one of the top 10 causes of mortality in children under-5 in TB-endemic areas.[2,3] To improve access to TB treatment for children, WHO released new consolidated guidelines on the management of TB in children and adolescents on World TB Day in March 2022.[4] The guidelines propose new evidence-based approaches to diagnosis in resource-limited settings, as well as universal availability of child-friendly, water-dispersible, fixed-dose combination tablets (FDCs) for treatment of TB disease and infection. The advantage of these tablets is that when a fraction of the dose is required, the tablets are dissolved in water and a fraction of the solution can then be administered. To close major gaps in DR-TB detection and treatment, the guidelines encourage first-line use of sensitive microbiological tests that detect TB and identify rifampicin resistance (such as Xpert MTB/RIF Ultra), as well as appropriate treatment of children with 'presumptive DR-TB'. These are children without bacteriologically confirmed DR-TB, but who have a clinical TB diagnosis and documented contact with an infectious DR-TB case who is the most likely source of infection.

The newer drugs, bedaquiline and delamanid, previously suggested but not endorsed for use in children with MDR-TB,[5,6] are now included as conditionally recommended for use with very low certainty of evidence. Recommendations to use the newer drugs also urges the use of child-friendly formulations, which was a previously unmet clinical need.[7] Recognition of this unmet clinical need prompted a global consortium of child TB researchers to set up a project called Better Evidence and Formulations for Improved MDR-TB Treatment for Children (BENEFIT Kids).[8] An aim of this project was to develop child-friendly formulations of TB drugs, with a focus on second-line drugs.

An article published in this issue of the Journal,[9] begins a series of articles that will provide details of new child-friendly, second-line TB drug formulations. These are now available through the Global Drug Facility (GDF), including bedaquiline, delamanid, pretomanid and clofazimine. Articles to follow in the series assess the taste and acceptability of these products in children and provide practical guidance to prescribers, pharmacists, and carers, on the optimal use of these drugs.

Historical situation of DR-TB disease and treatment in children aged ≤10 years

DR-TB strains emerged soon after the first TB drugs became available in the 1940s.[10] The demonstration that acquired drug resistance could be minimised with adherent, quality-assured multi-drug therapy provided strong motivation for the DOTS strategy.[11] However, while implementation of the DOTS strategy cured millions of TB patients and averted many TB deaths, DR-TB continued its disconcerting rise, with potential for epidemic replacement in the absence of concerted efforts to limit the spread of DR-TB.[12,13] The "fitness cost" observed with drug resistance acquisition[14] in the laboratory provided a false sense of security, with initial underappreciation of the risk for the potential epidemic spread of DR-TB strains.[15] Proof of MDR-TB transmission in New York City[16] and an outbreak of extensively drug-resistant TB (XDR-TB) in Kwazulu Natal, South Africa,[17] provided strong evidence of highly virulent DR-TB strains able to spread within communities (at least among immune-compromised patients). The increased availability of strain typing, and more recently, whole-genome sequencing, allowed more accurate descriptions of DR-TB spread also within communities with low rates of HIV infection, with proof of multi-decade evolution in some clinical settings.[18–20] DR-TB transmission puts children at risk, because children develop TB after exposure to an infectious source case, and childhood TB reflects transmission within households and communities.[21]

For the first time in decades, there are new oral drugs available for DR-TB treatment that have the

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potential to transform patient care. In the past, children with DR-TB were left behind when new advances in therapy were implemented. This was partly due to the unavailability of child-friendly drug formulations, and their routine exclusion from clinical trials for TB treatment and prevention. This led to an NIH consensus statement on the earlier inclusion of children in TB drug development and trials.[22] It was also recognised that we need better pathways to improve children's access to new treatment options.[7] With good treatment access, children with DR-TB generally have excellent treatment outcomes (better than adults).[23] However, children had to wait many years before they could access new therapeutic advances for adult TB patients. It is wonderful to see that children will benefit from these recent exciting developments, and the data presented provide some of the evidence required for effective and efficient use (such as the tolerability, safety and optimal dosing of new drugs). When considering the changing TB treatment landscape for children, it is important to consider specific therapeutic challenges when treating central nervous system disease, which occurs more commonly in young and vulnerable children than in adults.[24]

Design, formulation and quality of paediatric formulations

In paediatric pharmacotherapy, dosing must be flexible and liquid preparations should provide maximum flexibility. For some drugs, water-dispersible tablets or oral liquid dosing forms are commercially available, but for most drugs these are not. One can choose to use the parenteral form orally; however, the taste is usually unpleasant, in which case the pharmacist is asked to prepare an oral liquid dosage form. As starting material, the pharmacist sometimes has the pure compound, but often a solid oral dosage form, such as a tablet or capsule, is all that is available. The main choice for a liquid preparation is between a drug solution and a drug suspension. An aqueous solution is usually preferred because of the uniform distribution of the drug and high dosing accuracy. However, aqueous solutions are only possible if the solubility of the drug or its salt is high. If a drug or its salt has a limited solubility, solvents other than water or co-solvents are required. Examples of co-solvents are propylene glycol, glycerol, sorbitol and ethanol. For paediatric patients, the amount of co-solvent that can be administered is limited. Cheaper but toxic diethylene glycol should never be used.[25] Less water-soluble drugs can also be suspended, which may also help to mask the unpleasant taste. Suspensions are heterogenous and unstable and need to be homogenised before use. To stabilise suspensions, the following preconditions must be met: 1) homogeneous primary particle size and no aggregation of particles; 2) right particle size ($<$180 μm); 3) increased viscosity and density of vehicle to reduce settling rate of particles; 4) intermediate nature of the sediment, between flocculated and deflocculated.

An example of a compound that can increase density is sugar syrup. Viscosity is increased by adding agar, tragacanth or Arabic gum. Commercially available vehicles for suspensions include Ora-Plus® (Medisca, Montreal, QC, Canada). In addition to the form, some additional aspects need attention:

Taste

Although oral suspensions can mask a bad taste, there is often an unpleasant after-taste, which can result in a reluctance to take the drug. In that case, flavouring agents can be added. To improve taste, several general principles apply: 1) a sour taste is improved by adding sweeteners or by a citric taste (lemon); 2) a bitter taste can be improved by adding a chocolate or vanilla flavouring; 3) a sweet taste can be improved using peppermint; 4) a salty taste can be improved with anise or liquorice.

Microbiological quality

As water supports the growth of micro-organisms, oral solutions and suspensions need to be adequately preserved. Sometimes co-solvents have preservative properties, such as propylene glycol, glycerol and high concentrations of sugar. Usually, preservatives such as methyl- and propylhydroxybenzoate, benzoic acid or sorbic acid are used. The choice of the preservative depends on the pH of the vehicle. Sorbic acid is preferred in a vehicle with a pH ranging from 4.5–5.5. Some excipients are less suitable for children, but information on these is sparse. The European and United States Paediatric Formulary Initiatives are working in collaboration to create a database Safety and Toxicity of Excipients for Paediatrics (STEP) containing specific safety and toxicity data.[26]

Physical stability

Due to their nature, suspensions have limited physical stability and sedimentation of the active compound can occur during storage. The monograph Unlicensed Medicines in the British Pharmacopea describes how to assess settling and resuspensibility.[27]

Chemical stability

Dissolved substances are more accessible for water than suspended substances. Degradation therefore occurs more rapidly in solutions than in suspensions. However, both types of oral preparations are exposed to water and hydrolysis can occur. Therefore, chemical stability testing needs to be performed at least as long as the proposed shelf life of the product. Analytical methods need to be stability-indicating,

and to prove suitability of the analytical method, forced stability tests need to be performed.

Shelf-life

Shelf-life depends on the results of the physical and chemical stability tests, but generally, must not exceed 1 month for extemporaneously prepared oral administration forms by pharmacists. In the United Kingdom, efforts have been made to standardise the use of oral liquid medicines to treat TB.[28] This is the case for several first-line anti-TB drugs, but for most second-line anti-TB drugs, guidelines are not yet available. Progress towards this is presented in the article by Taneja et al., which describes stable sugar and sugar-free suspensions of pretomanid.[9] Pretomanid tablets were crushed (using a mortar and pestle) until a fine powder. Simple syrup (sugar-containing formulation) and Thick & Easy® (sugar-free formulation; Fresenius Kabi Ireland, Dublin, Ireland) were mixed with the powder, and the resulting suspension stored in standard plastic prescription bottles. Stability studies indicated that the product could be kept at ambient room temperature and at 30°C for a period of 30 days. Currently, pretomanid is only approved for adults, and its potential reproductive toxicity has delayed trials in children.[29] Data from recent studies have demonstrated that pretomanid is not associated with testicular toxicity,[30] which should facilitate further evaluation in children. For now, the demonstration that pretomanid suspensions are feasible and stable can be applied in older patients with dysphagia, but it also makes it available for further testing and potential compassionate use in children. Despite the relatively small market, there is a huge clinical need for liquid dosing of second-line TB drugs that are suitable for children.[31] Given the lack of commercial interest to develop such products, the BENEFIT Kids[8] initiative provides an example of how a valuable evidence base for the provision of high-quality oral liquid dosing forms can be built in instances of market failure.

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References

1 World Health Organization. Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021.
2 Dodd PJ, et al. The global burden of tuberculosis mortality in children: a mathematical modelling study. Lancet Glob Health 2017; 5(9): e898-e906
3 Jenkins HE, et al. Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2017; 17(3): 285-295
4 World Health Organization. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO, 2022.
5 Das M, et al. New TB drugs for the treatment of children and adolescents with rifampicin-resistant TB in Mumbai, India. Int J Tuberc Lung Dis 2020;24(12):1265–1271.
6 Seddon JA, et al. Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis. Lancet Respir Med 2018;6(9):662–664.
7 Brigden G, et al. Getting it right for children: Improving tuberculosis treatment access and new treatment options. Expert Rev Anti Infect Ther 2015; 13(4): 451-461
8 Better evidence and formulations for improved MDR-TB treatment for children (BENEFIT Kids). http://blogs.sun.ac.za/dttc/benefit-kids/.
9 Taneja R, et al. Stable sugar and sugar-free suspensions of pretomanid. Int J Tuberc Lung Dis 2022; 26:1112–1117.
10 Mitchison D, Davies G. The chemotherapy of tuberculosis: Past, present and future. Int J Tuberc Lung Dis; 16(6): 724-732
11 Raviglione M C, Pio A. Evolution of WHO policies for tuberculosis control, 1948–2001. Lancet 2003; 359(9308): 775-780
12 Raviglione M, et al. Scaling up interventions to achieve global tuberculosis control: Progress and new developments. Lancet 2012; 379(9829). 1902-1913
13 McBryde ES, et al. The risk of global epidemic replacement with drug-resistant *Mycobacterium tuberculosis* strains. Int J Infect Dis 2014; 56. 14-20
14 Middlebrook G, Cohn ML. Some observations on the pathogenicity of isoniazid-resistant variants of tubercle bacilli. Science 1979;118:3063. 297-299
15 Toungoussova OS, et al. Impact of drug resistance on fitness of *Mycobacterium tuberculosis* strains of the W-Beijing genotype. FEMS Immunol Med Microbiol 2004; 42(3). 281-90
16 Moss AR, et al. A city-wide outbreak of a multiple-drug-resistant strain of *Mycobacterium tuberculosis* in New York. Int J Tuberc Lung Dis 1997; 1(2): 115-121
17 Gandhi NR, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575–1580.
18 Marais BJ, Sintchenko V. Epidemic spread of multidrug-resistant tuberculosis in China. Lancet Infect Dis 2017; 17(3): 238-239
19 Bainomugisa A, et al. Multi-clonal evolution of multi-drug-resistant/extensively drug-resistant *Mycobacterium tuberculosis* in a high-prevalence setting of Papua New Guinea for over three decades. Microb Genom 2018; 4(2): e000147
20 Marais BJ, et al. Epidemic spread of multidrug-resistant tuberculosis in Johannesburg, South Africa. J Clin Microbiol 2013; 51(6). 1818-25
21 Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med 2012;367:348–361.

22 Nachman S, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis 2015;15(6):711–720.
23 Harausz EP, et al. Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis. PLoS Med 2018;15(7): 1002591.
24 Huynh J, et al. Tuberculosis treatment in children: the changing landscape. Paediatr Respir Rev 2020; 36. 33-43
25 Schep LJ, et al. Diethylene glycol poisoning. Clin Toxicol 2009; 47(6). 525-535
26 European Paediatric Formulation Initiative. Safety & Toxicity of Excipients for Paediatrics (STEP) database. London, UK: EuPFI, https://step-db.ucl.ac.uk/eupfi/appDirectLink.do?appFlag=login.
27 British Pharmacopoeia Commission. British Pharmacopoeia, 2016. London, UK: BPC, 2016.
28 Lowey A, Chapstick, T. Standardising the use of oral liquid medicines to treat tuberculosis in the UK. Pharmaceutical J 2018. DOI 10.1211/CP.2018.20204497
29 Burke A, Alffenaar J, Denholm J. Evidence of safety for pretomanid and male reproductive health. Int J Tuberc Lung Dis 2022;26(6):473–474.
30 Boekelheide K, et al. Male reproductive hormones in patients treated with pretomanid. Int J Tuberc Lung Dis 2022;26(6): 558–565.
31 Marais BJ, et al. Paediatric tuberculosis – new advances to close persistent gaps. Int J Infect Dis 2021; 113: S63-S67