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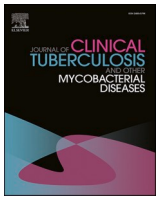

Multidrug-resistant tuberculosis in children: A practical update on epidemiology, diagnosis, treatment and prevention

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ABSTRACT

Pediatric multidrug-resistant tuberculosis (MDR-TB) remains a significant global problem, and there are numerous barriers preventing children with MDR-TB from being identified, confirmed with microbiologic tests, and treated with a safe, practical, and effective regimen. However, several recent advances in diagnostics and treatment regimens have the promise to improve outcomes for children with MDR-TB. We introduce this review with two cases that exemplify both the challenges in management of MDR-TB in children, but also the potential to achieve a positive outcome. More than 30,000 cases of MDR-TB per year are believed to occur in children but less than 5% are confirmed microbiologically, contributing to poorer outcomes and excess mortality. Rapid molecular-based testing that provides information on rifampin susceptibility is increasingly globally available and recommended for all children suspected of TB disease–but remains limited by challenges obtaining appropriate samples and the paucibacillary nature of most pediatric TB. More complex assays allowing better characterization of drug-resistant isolates are emerging. For children diagnosed with MDR-TB, treatment regimens have traditionally been long and utilize multiple drugs associated with significant side effects, particularly injectable agents. Several new or repurposed drugs including bedaquiline, delamanid, clofazimine and linezolid now allow most treatment regimens to be shorter and all-oral. Yet data to support short, all-oral, novel regimens for young children containing pretomanid remain insufficient at present, and there is a compelling need to conduct pediatric trials of promising therapeutics and MDR-TB treatment regimens.

1. CASE 1: Chandigarh, India

An 11-year-old girl presented to hospital during her ninth month of first-line anti-tuberculous treatment (ATT) with isoniazid, rifampin, pyrazinamide, and ethambutol for presumptive pulmonary tuberculosis (TB) based on abnormal X-ray findings and household contact to active TB. Two relatives (paternal uncle and aunt) had died from tuberculosis a year prior to her illness. A history of chronic, intermittent diffuse abdominal pain and weight loss was noted as well as more recent symptoms including vomiting, loose stools, altered sensorium and inability to walk. On examination she was severely emaciated (weight: 12 kg, height 130 cm) and pale. She had multiple matted, non-tender, lymph nodes palpable in posterior triangle of neck. There was bilateral pitting pedal edema and digital clubbing. Her abdomen was distended and slightly tender with presence of shifting dullness but no organomegaly. Breath sounds were reduced bilaterally with dullness on percussion. She had altered sensorium (Glasgow coma scale was 9/15), 4-extremity hypotonia, and absent deep tendon and plantar reflexes. There was no obvious cranial nerve palsy, and no neck rigidity. Laboratory investigations showed anemia, thrombocytopenia, leukocytosis, hypoalbuminemia. Imaging features were suggestive of pulmonary TB with pulmonary thromboembolism, intestinal involvement, and embolic

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infarcts in brain. A Xpert MTB/RIF done on a gastric lavage sample detected *Mycobacterium tuberculosis* (MTB) with rifampin resistance.

The patient was started on second-line ATT comprised of two World Health Organization group A drugs (linezolid and levofloxacin), two group B drugs (cycloserine and clofazimine) and two group C drugs (amikacin and ethambutol) [1]. Bedaquiline was not started as her weight was 11 kg, below the minimum weight of 15 kg required to start the drug in accordance with Drug-Resistant-TB (DR-TB) program guidelines of India in 2021. She received supportive care and nutritional support and was discharged from hospital after 3 weeks. Her gastric lavage sample culture subsequently showed growth of MTB. First- and second-line drug line probe assays (LPAs) demonstrated *katG* and *InhA* mutations denoting resistance to isoniazid, and a *gyrA* gene mutation denoting resistance to fluoroquinolones. The isolate was genotypically sensitive to aminoglycosides. Liquid-media sensitivity testing showed additional resistance to pyrazinamide. Levofloxacin was stopped and she continued linezolid, clofazimine, cycloserine, amikacin and ethambutol. The amikacin was given daily for three months and then on alternate days for three months; hearing assessment before and after amikacin therapy was normal. She was continued on linezolid, cycloserine, clofazimine and ethambutol. The child responded well to treatment with weight gain, reduced cough, and improved abdominal pain. Repeat gastric lavage after 3 months showed no growth of MTB. Repeat imaging after 16 months of therapy showed resolution of brain infracts and pulmonary thrombus, but presence of fibrocalcific and fibronodular changes in the lungs and intestinal short segment mural thickening, both suggestive of healed disease. At the time of this report the child is in her 17th month of ATT with a plan to repeat cultures before stopping therapy at 18 months.

2. CASE 2: Rochester, Minnesota, U.S.

A 14-year-old male presented with epistaxis, cough, and hemoptysis. His family history was significant for a parent who had been treated for pulmonary tuberculosis three years prior. The parent's TB isolate was initially isoniazid mono-resistant but developed additional culture-confirmed rifampin resistance in the setting of poor initial treatment compliance. The child converted from negative to positive interferon-gamma release assay (IGRA) 6 months after his initial contact evaluation—timing suggestive of exposure following development of rifampin resistance. His family declined LTBI treatment and elected to undergo medical monitoring, and he was lost to follow-up after 18 months. Two years later he presented following an episode of hemoptysis and worsening cough. His chest x-ray had a new right upper lobe opacity and given clinical symptoms, chest x-ray findings, and known previous exposure, reactivation of his drug-resistant-LTBI was suspected. A chest CT confirmed multiple pulmonary opacities, calcified right hilar and mediastinal lymph nodes, and no evidence of cavitation. Laboratory evaluation included a normal complete blood count (CBC), complete metabolic profile (CMP), CRP and ESR. HIV antibody/antigen screen was nonreactive. Testing for endemic fungi and viral agents was normal. ECG was normal. Multiple sputum specimens were collected, and all were acid-fast smear and MTB PCR negative. His family declined bronchoscopy.

A repeat CT revealed progressive disease. The combination of worsening imaging, known exposure, and clinical course were concerning for pulmonary tuberculosis despite negative microbiologic testing. His family was very reluctant to start treatment and discussions were impacted by significant cultural and linguistic barriers. Given the previous family history of poor compliance, prior declination of LTBI treatment and loss to follow-up after exposure, there were significant concerns for compliance with a complex, prolonged or high-side effect regimen. Therefore, after extensive discussion of the uncertainties of the regimen in children, he was initiated on bedaquiline, pretomanid, and linezolid (BPaL) by weekday directly observed therapy (DOT) and asynchronous weekend video DOT. Dosing based on his weight of 45 kg was bedaquiline 400 mg once daily for 2 weeks followed by 400 mg three times weekly, pretomanid 200 mg once daily and linezolid 600 mg daily.

Follow up chest x-ray six weeks after treatment initiation demonstrated improvement, though not resolution of right upper lobe opacities. A CT scan two months after treatment initiation demonstrated interval cavitation but overall improvement. He continued to do well clinically without fever, chills, night sweats, cough, or hemoptysis. He denied side effects of his medication regimen including nausea, vomiting, diarrhea, headache, rashes, changes in vision, palpitations, weakness, or tingling. He did express mild depressive symptoms early in treatment which resolved after he was able to increase his activities and be less isolated. CBC, CMP, and liver enzymes all remained normal on serial assessment. There was no QTc abnormality noted on monitoring EKG. Therapeutic drug monitoring (TDM) was performed on two occasions: at approximately 1 month of treatment his linezolid 25-hour trough was 0.55 mcg/mL, pretomanid 25-hour trough was 1.88 mcg/mL and bedaquiline 50-hour trough was 0.73 with a n-monodesmethyl bedaquiline of 0.43 mcg/mL, all within target ranges. At 2 months of therapy, linezolid 2-hour peak was 9.94 mcg/mL, and 24-hour trough was 2.12 mcg/mL; bedaquiline and pretomanid were not assessed. There were no dose adjustments made on the basis of TDM.

The patient completed 26 weeks of daily therapy and chest x-ray at the end of treatment demonstrated the right upper lobe mild nodular and streaky opacities had further decreased in size but not completely resolved. Chest x-ray 6 months after treatment demonstrated continued subtle improvement and no new abnormalities.

3. Epidemiology of pediatric MDR-TB

According to the WHO, in 2021 there were an estimated 10 million people worldwide with tuberculosis (TB) disease, 1.2 million of whom were children < 15 years of age [2]. Children also account for approximately 14 % of the 1.4 million TB deaths internationally and most childhood disease and death occurs in low- and middle-income countries [3,4]. Worldwide, TB in children has long been a neglected disease, so cases are often unrecognized and case counts remain an estimate. The reasons for this include lack of public health resources devoted to identifying pediatric cases and inherent health disparities and adverse social determinants of health among populations at risk of TB, as well as insufficient diagnostic tools to identify disease in children who often have paucibacillary disease, inability to expectorate sputum, and extrapulmonary disease. Thus, it is particularly challenging to determine the burden of multidrug resistant-TB (MDR-TB) in children. This is made even more difficult by limited access to resistance testing and treatment regimens for MDR-TB. It is estimated that globally only 3–4 % of pediatric MDR-TB cases are diagnosed and treated, with 22 % of children dying as a result of their infection [5].

Several researchers have attempted to determine the global burden of MDR-TB in children through different modeling studies. A 2014 study estimated 32,000 annual incident pediatric MDR-TB cases, and also found that the proportion of children with incident MDR-TB in any one setting reflects the proportion of adult incident cases in that same setting [6]. An alternate model in 2016 predicted 25,000 annual incident pediatric MDR-TB cases globally [3]. Both studies found that pediatric MDR-TB accounted for approximately 3 % of all pediatric TB, far more than what had previously been diagnosed or treated. WHO regions with higher rates of MDR-TB in the general population also have higher rates in children. A study from South Africa found a prevalence of pediatric MDR-TB of 8 % while another from China showed that among children with TB 18.9 % had drug-resistant (DR)-TB and 6.9 % had MDR-TB [7,8]. A *meta*-analysis of MDR-TB reports in children found a much higher rate of MDR-TB among middle income countries (lower-middle-income countries: 6.3 %; upper-middle-income countries: 7.3 %) compared to high-income countries (1.8 %) [9].

The burden of MDR-TB in children is a function of the burden of MDR

LTBI. Knight et al. in 2019 used World Health Organization (WHO) data to estimate the global incidence of latent TB infection due to drug-resistant MTB found a prevalence 2.9 % among children < 15 years, which was significantly higher than that of the total population (1.2 %) [7]. The highest proportion of LTBI in children due to MDR MTB occurred in the WHO European region (14.1 %) with other regions having between 2–4 %; prevalence was increasing in all WHO regions.

In the U.S., TB cases in children account for approximately 4 % of total TB cases [10]. The highest rates of childhood TB are in immigrants, international adoptees and refugees from high-prevalence regions as well as children with close contact to non-US-born adults from TB endemic countries [11]. Identifying U.S. children with MDR-TB is important for management of the child as well as recognizing recent transmission in the community. A survey of the US National Tuberculosis Surveillance System (NTSS) from 1993 to 2014 showed that of culture confirmed pediatric TB, 1.7 % of children (82 total) had MDR-TB with 1–6 pediatric MDR-TB cases reported annually [12]. This prevalence was similar to the overall prevalence in the U.S. Two-thirds of children were US-born, indicating transmission of MDR-TB within the US, and most children had pulmonary TB only. Of the 82 confirmed MDR-TB cases, 66 (81 %) had resistance to first-line drugs in addition to rifampin and isoniazid, and one third (24/73) had resistance to at least one second-line drug. Importantly, 9 % of MDR-TB cases had fluoroquinolone (FQ) resistance and 6 % had resistance to FQ plus an additional injectable agent.

Children most often acquire MDR-TB from close adult or adolescent contacts, typically, but not exclusively, in a household. A study from Peru showed children exposed to MDR-TB at home had TB disease rates approximately 30 times higher than children in the general population [13]. A *meta*-analysis looking at yield of contact investigations of patients with DR-TB found that 4 % and 27.3 % of pediatric contacts developed active and latent TB respectively [14]. These studies serve to reinforce the importance of public health infrastructure for initial diagnosis of TB cases and contact investigations as a tool to slow the spread of MDR-TB.

The COVID-19 pandemic has had a significant impact on the burden of TB worldwide. According to the WHO there was a 4.5 % global increase in the incidence of TB in the general population between 2020 and 2021 with a 3 % increase in DR-TB [15]. This was accompanied by a decline in global spending for TB services. In 2022, there was a recovery in numbers of patients diagnosed and treated with TB, but treatment starts for MDR-TB remained below pre-pandemic levels. Children may have been affected by the COVID-19 pandemic in several ways including misdiagnosis of TB as COVID-19, delayed diagnosis due to public health resources that shifted from TB to COVID-19, disrupted TB program and health system capacity, and prolonged exposures to adult contacts whose diagnosis was also delayed. Caregivers may have also been hesitant to seek care for an ill child due to concern for coming into contact with SARS-CoV-2. The full impact of the pandemic on TB including MDR-TB in children has yet to be established though a recent study suggests that after years of increasing TB notification counts in children, global notifications were 35.4 % lower than predicted for children 0–4 years old in 2020 [16].

4. Diagnostic considerations for pediatric drug-resistant tuberculosis

There are several instances in which DR-TB should be considered in children—most notably when the child is in contact with a microbiologically-proven case of DR-TB or when drug resistance in a contact is suggested based on clinical information (for instance, if the source case had a treatment failure, required retreatment or died from TB). Drug resistance should also be suspected when the pediatric patient is not responding to first-line therapy despite good adherence, if a child previously treated for TB presents with disease recurrence, or if the child is part of a community with links to countries in the WHO global lists of high burden countries for MDR-TB or a local community where MDR-TB has been detected [15]. When DR-TB is suspected, every effort should be made to confirm the diagnosis by obtaining specimens for culture and drug susceptibility testing (DST) but it is important to recognize that young children often cannot produce sufficient sputum samples and develop paucibacillary respiratory or extrapulmonary disease making microbiologic-confirmation difficult. Thus, all available microbiological data should be obtained from the (frequently adult) source case if known.

4.1. Pediatric tuberculosis: General diagnostic considerations

In recent years there have been several important advances in TB diagnostics with implications for the approach to microbiologic confirmation and detection of resistance in children [17]. The current recommendation from the WHO is to use Xpert MTB/RIF or Xpert MTB/RIF Ultra as the initial diagnostic test for TB detection and identification of rifampin resistance in sputum specimens, in place of conventional approaches such as microscopy and culture-based DST [18]. The pooled sensitivity of the Xpert MTB/RIF in a recent WHO *meta*-analysis was 64.6 % (95 % Confidence interval (CI) 55.3 to 72.9) compared to a microbiologic standard, and 19.7 % (95 % CI 12.1 to 30.4) compared to a composite standard; specificity was 99.0 % (95 % CI 98.1 to 99.5) for microbiologic standard and 100 (95 % CI 100–100) for composite standard [18]. In the case of Xpert MTB/RIF Ultra (currently not available in the U.S.), diagnostic sensitivity is improved—particularly among paucibacillary samples—over the Xpert MTB/RIF through inclusion of two multicopy gene targets (IS1081 and IS6110) in addition to the *rpoB* gene [19]. Samples that are positive for these genes but negative for *rpoB* result in a "trace call" result, which, despite slight decreases in specificity, should be considered positive results for children, persons living with HIV and in extrapulmonary specimens [18]. Though data on the performance of the Ultra assay are still relatively sparse in pediatric patients (3 studies with approximately 700 participants), the pooled sensitivity was 72.8 % (95 % CI 64.7 to 79.6) and specificity was 97.5 % (95 % CI 95.8 to 98.5) and 23.5 % (95 % CI 20.0 to 27.4) and 99.2 % (95 % CI 96.9 to 99.8) compared to a microbioligc and composite standard, respectively. These assays may be used on sputum, nasopharyngeal aspirates, gastric aspirates, or stool for children with suspected pulmonary TB, and on cerebrospinal fluid, lymph node biopsy, pleural, pericardial and peritoneal fluids, and urine for extrapulmonary TB, and in blood for suspected disseminated TB among children living with HIV infection [20].

Stool collection is non-invasive and practical, and thus a compelling sample type for children. A recent systematic review and *meta*-analysis of stool Xpert MTB/RIF found pooled sensitivity and specificity against a microbiologic reference standard of 67 % (95 % CI, 52 to 79 %) and 99 % (95 % CI, 98 to 99 %), respectively; sensitivity among children living with HIV was 79 % (95 % CI, 68 to 87 %) [21]. A previous barrier to more widespread adoption of PCR testing in stool was complex dilution and filtratration requirements for sample processing prior to testing, but a more straightforward and less resource intensive method known as the Simple One-Step (SOS) has been validated, and its performance demontrated in the clinical setting [22]. Future research will be needed to define optimal implementation of stool PCR testing. Because of a high positive predictive value, a positive result, particularly when it indicates rifampin resistance, is a high-value outcome while a negative result cannot be used to rule out TB because of a low negative predictive value. WHO estimates it is likely to be cost effective to perform stool PCR in countries with TB prevalence > 3 % when used in situations where no additional diagnostic testing is performed [20].

4.2. Diagnostic considerations specific to MDR-TB in children: rapid/initial tests

Identification of rifampin resistance using Xpert MTB/RIF or Ultra

provides essential information for initiating an effective treatment regimen, but there are notable limitations to relying on these assays for MDR-TB/RR-TB detection. Among these is the obvious limitation in susceptibility prediction to rifampin only. Furthermore, "trace call" results are reported as having indeterminate rifampin susceptibility because the rpoB gene is not detected. Due to the paucibacillary nature of pediatric TB, a significant proportion of Xpert Ultra results will be trace call. Multiple studies have noted a frequency of approximately 20 % trace call results in pediatric sputum samples and higher rates are observed in non-sputum samples [23–24]. For example, one study of 447 children noted an overall sensitivity in stool for the Xpert Ultra of 83.3 % among bacteriologically-confirmed cases, but 80.0 % of these were trace call and would therefore give no additional information regarding drug resistance [25]. There is insufficient data to determine the sensitivity and specificity of Xpert Ultra for detection of rifampin resistance in children or to compare performance to Xpert MTB/RIF, on any specimen type Kay et al., 2022;9 [26].

The Truenat MTB-RIF Dx assay, developed by Molbio in India, represents an additional point-of-care method for the detection of MDR-TB using sputum samples, particularly in low-resource primary healthcare settings. Its applicability is limited to individuals with positive results from the Truenat MTB or MTB Plus tests. With diagnostic performance comparable to that of the Xpert MTB/RIF assay for diagnosing pediatric tuberculosis in sputum samples, it is included in WHO guidelines as an acceptable alternative initial test for TB detection and rifampin resistance [18].

There are an increasing number of available rapid diagnostic technologies that provide additional drug susceptibilitiy data. The class of moderate complexity automated NAATs including the Abbott RealTime MTB RIF/INH (Abbott Molecular, USA), BD MAX™ MDR-TB (Becton Dickinson, USA), FluoroType® MTBDR (Bruker-Hain, Germany) and the cobas® MTBRIF/INH (Roche, Switzerland) are generally available outside the U.S. and can be used in sputum samples for the detection of TB and resistance to rifampin, but also include targets for *katG* and *inhA* mutations which confer resistance to isoniazid. These assays may be used for pediatric sputum samples, though test performance characteristics (generally very high sensitivity and specificity) are mostly extrapolated from adult data at present [27].

4.3. Diagnostic considerations specific to MDR-TB in children: higher complexity testing

In all cases of confirmed MDR-TB on initial testing, further DST should be performed to exclude XDR-TB and to help establish an effective treatment regimen. Culture-based DST remains an important component of MDR-TB diagnostic evaluation in many settings, despite disadvantages related to requirements for technological expertise, biosafety and slow result turn-around. This is particularly true for detection of resistance to newer and repurposed drugs including the fluoroquinolones, bedaquline, linezolid and delaminid. In addition to detecting resistance to rifampin, several products provide molecular resistance testing for other anti-TB drugs. First-line line-probe assays (LPAs) detect resistance to rifampin, isoniazid, and fluoroquinolones. Second-line LPAs can provide additional information for detecting resistance to injectable drugs (amikacin, kanamycin, and capreomycin). Low-complexity automated NAATs, including the Xpert MTB/XDR assay (Cepheid, USA), can detect additional resistance to fluoroquinolones, ethionamide and second-line injectable drugs. High-complexity reverse hybridization-based NAATs can also detect resistance to pyrazinamide; sensitivity of these assays in a 2021 WHO *meta*-analysis was 81 % (95 % CI 75.4 to 85.8) compared to phenotypic drug susceptibility testing (which itself may overcall pyrazinamide resistance) [27–28]. Most of the tests require technical and biosafety resources that are available only in referral laboratories and typically require either MTB cultured isolates or at a minimum smear- or NAAT-positive samples and cannot be performed on stool. Thus, access to these platforms continues to be limited by the lower microbiologic yield in children with TB disease compared to adults.

In contrast to probe-based assays, next-generation sequencing (NGS)-based assays can provide detailed and accurate sequence information for the whole genomes of mycobacterial species, including whole-genome sequencing (WGS), pyrosequencing, and targeted NGS for detecting extensively drug-resistant (XDR)-TB. These approaches have largely replaced line-probe assays in the U.S. and other high-resource countries where a preferred approach is a low-complexity NAAT followed by a sequencing-based DST [29]. One example is the Molecular Detection of Drug Resistance (MDDR) service provided by the Centers for Disease Control and Prevention in the U.S, that utilizes targeted NGS supplemented by growth-based DST. This service is available free of charge through the U.S. public health laboratory system and is accessed via state and local public health TB programs. Information is available at: https://www.cdc.gov/tb/topic/laboratory/mddr-user-guide.htm#intro. Acceptable samples for this service include NAAT-positive sediment, pure *Mycobacterium tuberculosis complex* (MTBC) isolates, or mixed cultures known to contain MTBC.

5. Therapeutics for pediatric MDR-TB

After a long period with few additions to the MDR-TB therapeutic armamentarium, the last decade has seen the development of new drugs, as well as a repurposing of several older medications, which together have the potential to transform the treatment of children with MDR-TB. An overarching theme of recent progress is the emergence of shorter duration, all-oral treatment regimens which allow for much wider dissemination, fewer required resources, higher likelihood of successful treatment completion and lower toxicity. However, despite progress, data to inform broader utilization of newer medications and regimens for children lags behind that which is available for adult patients. In this section, several of these newer or repurposed medications are described individually, followed by identification of several resources available to pediatric clinicians building a pediatric MDR-TB treatment regimen.

5.1. Bedaquiline

Bedaquiline is a diarylquinolone that inhibits mycobacterial ATP synthase, providing potent bactericidal activity and sterilization [30]. Two pediatric studies have demonstrated that children, including those < 6 years have similar PK and safety profiles and informed the current WHO recommendation for use of bedaquiline for all ages as a component of MDR-TB treatment regimens, and provision of age and weight based-dosing (Table 1) [31–32], (IMPAACT p1108, data not published but reviewed by WHO)) Bedaquiline dosing is less well-established in children compared to adults. Currently, bedaquiline dosing recommendations in the pediatric population are based on age and weight to account for known PK/PD differences compared to adults. Bedaquiline is primarily undergoes oxidative metabolism in the liver (e.g., CYP3A4 metabolism), and given that the pediatric CYP450 enzyme is less mature compared to adults, bedaquiline clearance is decreased [30]. The current WHO recommendations account for the decreased bedaquiline clearance with overall lower doses in pediatric patients. Currently, pediatric bedaquiline dosing scheme mimics the adult bedaquiline dosing frequency of daily for the first 2 weeks (load), then 3 times a week (maintenance) [30]. Bedaquiline dosing guidance in pediatric patients may change as further evidence emerges [32]. The 20-mg tablet is scored and may be cut in half, crushed, and mixed with soft food, or dispersed in water and given through a feeding tube. Oral bioavailability is significantly enhanced up to 95 % when taken with food. Once absorbed, bedaquiline widely distributes into peripheral tissues. The slow release of bedaquiline and its metabolite from peripheral tissues is thought to contribute to an extremely long half-life (164 days (range 62–408) after 8 weeks standard TB dosing) [33]. The prolonged persistence even after cessation has implications for side effects

Table 1
Pediatric MDR-TB antibiotics.

Medication	Usual Dosing	Formulation[29]	Considerations
Moxifloxacin	10–15 mg/kg/dose every 24 h (max dose: 400–800 mg)	IV	Non-dissolvable tablets can be crushed and suspended in water for immediate administration. Crushed tablets have bitter taste and may not be tolerated.[15]
		Tablet (100 mg (dissolving), 400 mg)	Administer 4 h before or 8 h after products containing magnesium, aluminum, iron, or zinc including antacids, sucralfate, multivitamins, and didanosine.
Levofloxacin	15–20 mg/kg/dose every 24 h (max dose: 1000–1500 mg)	IV	Non-dissolvable tablets may be crushed and suspended in water for immediate administration.
		Oral Solution	
		Tablet (100 mg (dissolving), 250 mg, 500 mg, 750 mg)	Administer at least 2 h before or 2 h after antacids containing magnesium or aluminum, sucralfate, metal cations (eg, iron), multivitamin preparations with zinc, or didanosine chewable/buffered tablets or the pediatric powder for solution.
Pretomanid	Age 14 years and older: 200 mg once daily Safety and effectiveness not established in pediatric patients < 14 years.	Tablet (100 mg, 200 mg)	IMPAACT 2034 study (NCT05586230) is a phase 1, multi-site, open-label, PK, safety, tolerability, and acceptability study of a singly-dose of pretomanid in pediatric patients.
Delamanid	Age- and weight-based: 3 to < 5 kg: 25 mg every 24 h 5 to < 10 kg: <3 months: 25 mg every 24 h ≥3 months: 25 mg every 12 h ≥3 months: 25 mg every 12 h 10 to < 16 kg: 25 mg every 12 h 16 to < 30 kg: 50 mg every morning and 25 mg every night ≥30 to < 46 kg: 50 mg every 12 h ≥46 kg: 100 mg every 12 h	Tablet (25 mg, 50 mg)	The 25-mg tablet is formulated as a non-scored, palatable, dispersible tablet that may be dispersed up to 10 mL of water per 25 mg. Dissolve for at least 30 s and mix gently. Additional 10 mL of water should be used to administer the residual dose. The 50-mg tablet may also be crushed and dispersed in 5 mL water (dose < 50 mg) or in 10 mL water (dose ≥ 50 mg), which may take up to 5 min to dissolve. To improve palpability, 5 to 15 mL of sugar syrup may be added. Additional 5 mL of water should be used to administer the residual dose. Halved or crushed 50-mg tablet can also be added to soft food (i.e., mashed banana, peanut butter, yogurt).[9]
Linezolid	5 to < 10 kg: 15 mg/kg/dose every 24 h 10 to 23 kg: 12 mg/kg/dose every 24 h >23 kg: 10 mg/kg/dose daily (max dose: 600 mg)	IV Oral suspension Tablet (150 mg (dissolving), 600 mg)	Tablet may be crushed if needed. Caution with tyramine containing foods, selective serotonin repute inhibitors (SSRIs), and monamine oxidase inhibitors (MAOIs) due to the risk of serotonin syndrome.
Clofazimine	2–5 mg/kg/dose every 24 h (max dose: 100 mg)	Capsule (50 mg, 100 mg) Tablet (50 mg, 100 mg)	May administer higher doses (e.g., double the dose (4–10 mg/kg/dose) every other day) if needed due to tablet/capsule size. For patients who can only obtain the capsule product and cannot swallow capsules whole or who need tube administration, capsules may be macerated in 15 mL of hot water (120°F). Manipulation of the capsules can result in staining any item that encounters the slurry.[28]
Bedaquiline	Age- and weight-based: **Loading (weeks 1–2)** <3 months: 30 mg daily 3 to < 6 months: 60 mg daily ≥6 months: 7 to < 10 kg: 80 mg every 24 h 10 to < 16 kg: 120 mg every 24 h 16 to < 30 kg: 200 mg every 24 h ≥30 kg: 400 mg every 24 h **Maintenance (weeks ≥ 3)** <3 months: 10 mg three times weekly 3 to < 6 months: 20 mg three times weekly ≥6 months: 7 to < 10 kg: 40 mg three times weekly 10 to < 16 kg: 60 mg three times weekly	Tablet (20 mg (dissolving), 100 mg)	20-mg tablet is formulated as a scored, dispersible tablet. There are three administration methods of the 20-mg tablet: 1) Take intact tablet or cut tablet in halve along the score line. 2) Crush tablet and mix with soft food. 3) Disperse tablet in water. May be given through a feeding tube. 100-mg tablet may also be crush if needed.[3]

(*continued on next page*)

Table 1 (*continued*)

Medication	Usual Dosing	Formulation[29]	Considerations
	16 to < 30 kg: 100 mg three times weekly ≥30 kg: 200 mg three times weekly		

attributed to bedaquiline which cannot be expected to resolve quickly, and for potential emerging resistance in the setting of incompletely treated or recurrent TB disease, as it essentially becomes a single drug in the system over time. Bedaquiline is hepatically metabolized to an active metabolite, primarily through CYP3A4 enzyme. The active N-desmethyl metabolite (M2) is about 5 times less potent then bedaquiline itself and has a similarly long half-life [34]. Notable adverse effects in the pediatric clinical trials of bedaquiline included arthralgia, nausea, abdominal pain, QTc prolongation, and hepatoxicity. Children generally tolerate bedaquiline better than adults [1]. Bedaquiline was FDA approved to treat children with pulmonary MDR-TB in 2019. The safety profile in pediatric was based on a phase 2, open-label, multicenter, single-arm study, in which the safety of bedaquiline assessment was based on week 24 analysis from 30 pediatric patients [31]. In the study, bedaquiline was generally well tolerated in pediatric patients. The most common adverse effects (>10 %) in patients age 12–17 years patients included arthralgias, nausea, and abdominal pain. The most common adverse effects (>10 %) in patients 5–11 years included elevated liver transaminases. Importantly, no serious cardiac events were reported.

5.2. Nitroimidazoles (delamanid, pretomanid)

Delamanid and pretomanid are prodrugs that are activated by a mycobacterial nitroreductase enzyme to inhibit mycolic acid synthesis and produce nitrogen radicals. The two mechanisms of actions allow for bactericidal activity against both active and dormant *Mycobacterium tuberculosis* [35–36]. In a phase 1, PK and safety trial in pediatric patients with MDR-TB, the delamanid safety profile in pediatric patient aged ≤ 17 years old was comparable to the adults; the most common adverse effects reported in the study included nausea, vomiting, upper abdominal pain, insomnia, and headache [37]). Delamanid is currently recommended to be dosed according to age and weight by WHO (Table 1; further pediatric dosing trials are underway [38–39]. For all ages except those under 3 months of age or weight < 5 kg, dosing of delamanid is twice daily, which may provide additional logistical challenges for provision of directly observed therapy (DOT), which is typically based on once-daily dosing of TB medications [38].

Pretomanid is FDA-approved as a component of novel MDR-TB regimens consisting of bedaquiline, pretomanid, linezolid with or without moxifloxacin. Pretomanid is not well studied in younger children—a phase I/2 trial planned for 2023 will evaluate pharmacokinetics after a single pretomanid dose [40]. A frequently mentioned concern with relevance to pediatric patients is the observation of testicular atrophy and impaired fertility observed in rodents treated with pretomanid, a phenomenon that has been observed with similarly-structured nitroimidazoles, including metronidazole [36]. However, reductions in human male reproductive hormone levels among patients treated with pretomanid-containing regimens were not observed in four clinical trials, summarized in a 2022 *meta*-analysis [41]. Additionally, in a paternity survey, 38 men previously treated with pretomanid for 4–6 months fathered 44 children (unpublished data, reviewed by WHO) [1]. A clinical trial assessing sperm counts in patients that were treated with pretomanid is underway [42]. Thus, there is no current evidence that pretomanid at therapeutic doses impacts fertility [43].

Delamanid and pretomanid are available as oral tablets. The oral bioavailability of both delamanid and pretomanid is enhanced when taken with a fatty meal [35–36]. Both drugs have a large volume of distribution, and limited murine data supports central nervous system penetration with pretomanid [44]. Adverse effects that require close monitoring include QTc prolongation, hepatotoxicity, peripheral neuropathy, nausea, vomiting, and abdominal pain. Night terrors associated with sleep disturbances were reported with delamanid. Emergence of psychiatric side effects should be monitored, especially if patient is on other medications with neuropsychiatric side effects, such as cycloserine. Night terrors should typically not be an indication of therapy change [38].

5.3. Fluoroquinolones

Fluoroquinolones are an important components of multi-drug resistant TB treatment. They target DNA gyrase, which when inhibited results in disruption of DNA synthesis and cell death [45–46]. Newer generation fluoroquinolones, levofloxacin and moxifloxacin, are preferred for treatment of TB due to increased potency and decreased likelihood to develop resistance [47]. Higher maximum doses have been utilized when there is low-level resistance, such as in the presence of a 90Val *gyrA* mutation that is typically associated with an moxifloxacin MIC of < 1, though the efficacy of this approach has recently been questioned [45]. The maximum dose for moxifloxacin is 15 mg/kg daily capped at 600–800 mg per dose and for levofloxacin is 20 mg/kg daily capped at 1250–1500 mg per day [48–50]. Modeling studies suggest that current dose bands may result in lower drug exposure in children and doses > 20 mg/kg daily may be more optimal [51–52]. Although moxifloxacin is a potential agent that may be added to the MDR TB regimen, if both levofloxacin and moxifloxacin are available, levofloxacin is preferred due to fewer known drug interactions, a better characterized pediatric safety profile, and more frequent use and current literature in children for TB and for other indications [50]. The main adverse effects noted by the 2022 WHO guidelines include sleep disturbances, gastrointestinal upset, arthralgia/arthritis, headache, idiopathic intracranial hypertension, and QT prolongation [1]. Although moxifloxacin is thought to have a greater propensity to prolong QTc compared to levofloxacin, it is important to monitor QTc when administered with other QTc prolonging medications (i.e. clofazimine, bedaquiline) regardless of the fluoroquinolone chosen. Monthly monitoring is recommended for the first few months until all drugs reach steady state which can take weeks to months due to long half-lives and then periodically thereafter [20].

5.4. Clofazimine

Clofazimine is a repurposed drug of the antimicrobial class of riminophenazines, and exact mechanisms of action and antimicrobial resistance are not well understood. Clofazimine dosing is based on capsule size and patient weight. Capsules are available in 50 and 100 mg and a usual weight-based range is 2–5 mg/kg/dose once daily. Capsules can be administered every other day or every two days if the mg/kg/day dose is too high. Higher doses may be considered in patients when there are concerns for absorption or if the capsules will be manipulated and some drug may be lost [50]. For treatment of non-tuberculous mycobacterial infections in children a dose range of 1–3 mg/kg/day is most commonly reported [53–54]. Clofazimine should always be administered with food and due to its high lipophilicity property, absorption can be significantly improved when administered with a high fat containing

meal. Once absorbed, it is rapidly distributed to the peripheral tissues with slow re-equilibrium back to the central compartment. Clofazimine has a very long half-life, with a median half-life of 34.2 days in adults (49.5 days for females and 21.8 days for males) [49,55]. As with bedaquiline, the long half-life may result in viable bacilli being exposed to subtherapeutic concentrations without protection against resistance from additional medications after treatment cessation; however, the clinical significance of this phenomenon is unclear. The long half-life of clofazimine also has implications for the time required for resolution of potential adverse effects. Notable clofazimine side effects include reddish-brown or blackish skin discoloration (slowly reversible after clofazimine discontinuation), ichthyosis, QT prolongation, and abdominal pain [20,56–57].

5.5. Linezolid

Linezolid is an oxazolidinone antimicrobial that inhibits protein synthesis by binding to the 50S ribosomal subunit and blocking formation of the initiation complex for protein synthesis. Resistance to linezolid develops by target mutations that modify this ribosomal subunit. The dosing recommendation for linezolid for use in MDR-TB is once daily and the total daily dose is reduced by $\geq$ 50 % (e.g., 10–15 mg/kg/day versus 30 mg/kg/day) compared to dosing recommendations for other infectious syndromes (e.g. osteoarticular infections, pneumonia). This typically results in increased tolerability and less adverse effects such as peripheral neuropathy, cytopenias, lactic acidosis, and optic neuropathy. Children tend to have fewer side effects than adults, however peripheral neuropathy may be hard to recognize in children and can be irreversible [58–59]. Other notable adverse effects include diarrhea, headache, nausea, and pancreatitis. If there is a concern for toxicity, therapeutic drug monitoring can be considered if accessible. Adjusting the daily dose to a goal trough level of $<$ 2 mcg/mL has been reported to reduce side effects [60]. However, appropriate AUC/MIC ratios should be maintained for efficacy. In some cases, temporary cessation of linezolid may be needed to assess for other causes or allow for count recovery as bone marrow suppression related to linezolid is usually reversible once therapy is stopped. If re-starting linezolid is necessary, a lower dose or increased dosing interval may be considered Mase et al., 2022;9 [61]:ofac500.. Co-administration of linezolid with pyridoxine can be considered in select clinical situations where the patient may benefit (i.e. HIV, malnutrition). The benefit of pyridoxine added to linezolid administration in pediatric patients with TB is not well-characterized. There are reports that pyridoxine may help with reversal of cytopenias, but there is no recommendation for co-administration in current WHO guidelines [1,62].

5.6. Building a treatment regimen for pediatric MDR-TB

In addition to familiarity with novel drugs that are available for the treatment of MDR-TB in children, there are several resources—including guidance from the WHO, the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, and the Curry International Tuberculosis Center—available to help clinicians determine an optimal regimen, including decisions about the components of the regimen as well as the duration.

The short, all oral regimens comprised of bedaquiline, pretomanid, linezolid (BPaL) and moxifloxacin (BPaLM) are perhaps the most notable recent advances in the treatment of MDR-TB, and they are currently endorsed by WHO for use in children 14 years of age and older. Data that informs use of these treatment regimens in adolescents come from key studies including the TB-PRACTECAL, Nix-TB and ZeNix trials which enrolled a small number of adolescent patients. The TB-PRACTECAL used an innovative trial design among patients with rifampin-resistant TB [63]. In the first phase, three regimens were assessed for 8-week culture conversion: BPaL—46 %, BPaLM—77 % and BPaL plus clofazimine (BPaLC)—67 %. BPaLM was then selected for a phase 2–3 non-inferiority trial compared with standard of care; the trial was stopped early as the regimen was demonstrated to be non-inferior and superior. The Nix-TB trial demonstrated high rates (90 %) of favorable outcomes among adults (lowest age enrolled was 17 years) with MDR-TB treated with BPaL, but peripheral neuropathy and myelosuppression were common and attributed primarily to linezolid dosed at 1200 mg daily [64]. The follow-up ZeNix trial demonstrated lower toxicity and continued high efficacy of BPaL with linezolid dosed at 600 mg daily [65].

Though there is no current guidance for the use of BPaL/M in children younger than 14, pre-teen/early teen patients—particularly if they are of adult body weight—may warrant consideration of the regimen if BPaL/M represents the safest or most effective regimen. In this context it is important to consider recognized toxicities and limitations of more traditional regimens when assessing the uncertainties of BPaL. At the current date, it is not appropriate to consider BPaL in younger children, particularly given uncertainties regarding dosing of pretomanid, but if initial pharmacokinetic and safety studies are reassuring, it may not be necessary in all cases to wait for conclusive clinical trial data, as there is little reason to believe that the shorter, all oral course will not be equally (or more) effective in children than have been demonstrated in adults.

For younger children and others for whom a short BPaL or BPaLM regimen is not appropriate, two approaches to MDR-TB treatment in children are suggested in to the most recent WHO guidelines from 2022 [1]. The preferred regimen for eligible children is a standardized shorter duration, all-oral, bedaquiline-containing regimen composed of 6 months of bedaquiline in addition to 4 months of a fluoroquinolone, ethambutol, high-dose isoniazid, pyrazinamide, clofazimine and either ethionamide or linezolid (linezolid is only given for 2 months) followed by 5 months of a fluoroquinolone, clofazimine, ethambutol and pyrazinamide, for a total of 9 months. The extremely long bedaquiline half-life allows drug exposure well after the drug is stopped. Children with severe or extensive disease, additional resistance to any component of the regimen (except INH) or exposure $>$ 1 month to a component of the regimen without confirmed susceptibility to that drug are not eligible for the standardized short regimen. This regimen is supported by programmatic data primarily from South Africa and recent evidence that bedaquiline-containing regimens are superior and safer than similar regimens using injectable medications [1,66]. For children unable to receive the preferred regimen, a longer and more traditional individualized regimen is recommended. Designing such regimens involves selecting drugs to which the isolate is known or suspected to be susceptible from a framework of drugs categorized into groups according to potency: Group A (bedaquiline, levofloxacin/moxifloxacin, linezolid), Group B (clofazimine, cycloserine/terizidone), and Group C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, amikacin/streptomycin, ethionamide/prothionamide, p-aminosalicylic acid). If a longer individualized regimen must be utilized the best approach to start with is bedaquiline, levofloxacin/moxifloxacin, linezolid and at least one agent from Group B. If only one to two Group A agents can be used, then both Group B agents should also be in the regimen. Finally, if the regimen cannot utilize medications from Group A and B alone, the Group C agents are added. At minimum, four anti-TB agents likely to be susceptible should always be utilized as part of the treatment plan. WHO recommended treatment durations for individualized regimens are 18–24 months, with some potential shortening for children with milder disease.

Guidance from the Sentinel Project on Pediatric Drug Resistant Tuberculosis outlines a similar approach to drug selection as the WHO individualized regimen, but with a few key differences, including a recommendation that regimens contain at least 4 drugs, with a 5th added for severe TB [67]. This is in contrast to the 7 drugs recommended in current WHO guidance. Sentinel Project guidance also expresses a preference for delamanid among group C medications if a regimen cannot be built using Group A or B drugs only. Additionally, the Sentinel Project suggests treatment durations as short as 6 months for non-severe

disease. Another resource for developing an effective regimen for MDR-TB in younger children is the Drug Resistant Tuberculosis: A Survival Guide for Clinicians, produced by the Curry International TB Center and California Department of Public Health [29]. A proposed approach recommends a fluoroquinolone (levofloxacin or moxifloxacin), linezolid and bedaquiline, plus at least one (for milder disease) or two (for more involved disease) drugs from among clofazimine, cycloserine, delamanid or pyrazinamide. Clinicians can consider dropping one drug (keeping the FQ, linezolid and BDQ) after 4 months. For children with pulmonary or lymph node disease a duration of 9 months (with consideration to limit 6 months of BDQ given the long half-life as in the WHO standard short course but acknowledging that there is no data comparing the two durations) is likely sufficient; longer courses are required for disseminated or more severe disease.

Pediatric TB formulations are available through Stop TB's Global Drug Facility (GDF) for more than 100 countries. Many high-income countries require more stringent regulatory approval which limits some ability to obtain medications; in the US for example, delamanid is available only through compassionate use programs, and clofazimine is an orphan drug available for children only under single patient emergency investigational new drug application through FDA [56].

5.7. Drug-resistant latent tuberculosis infection in children

Tuberculosis preventive treatment (TPT) is of particular importance in the context of MDR-TB, but until recently there has been no standard approach to drug resistant latent tuberculosis in children. Limited studies in children have demonstrated that preventative treatment of drug resistant LTBI is effective [68]. Very young children and adolescents have higher rates of progression from infection to TB disease, a factor which should be considered when assessing risks, benefits and uncertainties related to drug-resistant LTBI treatment. Results from two recently concluded clinical trials have now provided critical data on the performance of levofloxacin-based TPT for both adults and children. The TB-CHAMP study was a cluster randomized trial enrolling 922 South African children < 5 years with household exposure to MDR-TB to either 6 months of levofloxacin (dose 15–20 mg/kg) or placebo, resulting in a 56 % reduction (5 cases (1.1 %) in treatment arm and 12 (2.6 %) in placebo arm) [69–70]. The VQUIN trial, conducted in Vietnam, randomized adults and children to 6 months levofloxacin or placebo and noted a 45 % reduction in TB cases [71]. These data informed a recent WHO rapid communication endorsing the use of levofloxacin for TPT for MDR-TB contacts of all ages [72]. Where resources exist to characterize resistance patterns of likely source cases and carefully monitore fluoroquinolone therapy, treatment of drug-resistant LTBI in children should be strongly considered. Where resources are more limited and source case identification and characterization is more difficult, logistical barriers currently limit wider utilization of drug-resistant LTBI treatment, levofloxacin TPT should be considered for high-risk individuals including children, particularly after a recent household contact with a case of MDR-TB [73]. Scant data inform approaches to LTBI due to drug-resistant TB that is also fluoroquinolone-resistant; an ongoing clinical trial is assessing tolerability and efficacy of delamanid for preventative treatment after household exposure among high-risk individuals, including children < 5 years of age [74]. A prospective cohort study conducted in Peru demonstrated a protective effect of INH-based TPT in primarily pediatric household contacts to MDR-TB, suggesting that INH may have a different mechanism of protection in LTBI than in treatment of active disease; these findings warrant further study and confirmation before widespread utilization of this strategy [75]. In all settings, infection control and public health efforts to limit transmission of MDR-TB are essential to preventive efforts.

6. Conclusion

The world has achieved significant progress toward a better capability to diagnose, treat and prevent MDR-TB in children, but the burden of disease and challenges remain significant. Clinical trials enrolling children continue to lag significantly behind the adult counterpart. The current status of pretomanid is a clear example: this drug has U.S. FDA approval for adults and multiple clinical trials demonstrating efficacy as part of a short all-oral regimen, yet pediatric studies are just commencing to assess dosing and safety. Even as diagnostic technologies and novel therapeutics become available, access remains inconsistent across regions, countries or among the most vulnerable populations in any given setting. And while an effective vaccine may one day have a "game-changing" influence on the global burden of TB, effective and practical candidates remain elusive. For the present, the intent of this "practical" review is to provide up-to-date and concrete information so clinicians can apply the best and current information in the care of children with suspected or proven MDR-TB.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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