Review

Pediatric Drug-Resistant Tuberculosis: The Current and Future Prospects for Management and Prevention

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Review

Paediatric Drug-Resistant Tuberculosis: The Current and Future Prospects for Management and Prevention

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Abstract: In the continued battle against one of the oldest enemies known to mankind, *Mycobacterium tuberculosis (MTB)*, the emergence of drug resistance among children poses multiple challenges for early detection and treatment. Molecular diagnostics and newer drugs like bedaquiline and delamanid have strengthened the armamentarium and helped design convenient, safe and child-friendly therapeutic regimens against drug-resistant tuberculosis (TB). Preventive strategies like treatment of TB infection among children living in close contact with patients with drug-resistant TB and effective vaccines against TB are currently in the investigative stages of development and implementation. In addition to the implementation of recent novel diagnostics and treatment modalities, effective psychosocial and nutritional support, as well as dedicated monitoring for compliance and adverse effects, are crucial determinants for successful treatment outcomes in these children.

Keywords: Bedaquiline (BDQ); Delamanid (DLM); Xpert MTB; tuberculosis; TB infection; latent TB; TB Vaccines; TB preventive treatment

1. Introduction

In the continued battle against one of the oldest enemies known to mankind, Mycobacterium tuberculosis (MTB), the emergence of drug-resistant TB (DR TB) in children poses multiple challenges for early detection and treatment.

A child is diagnosed with DR TB after navigation of a sequence of complex steps including accurate clinical suspicion, appropriate clinical and radiological testing, effective specimen collection and whenever possible, microbiological confirmation. Each of these steps has its own set of challenges among children. The clinical clues of chronic cough need to be differentiated from prolonged cough in post-viral illnesses and the hyperactive airway diseases which are common among children. A long list of differentials for inadequate weight gain or recurrent abdominal pain requires the clinician to be able to narrow down the differential diagnosis to suspect tuberculosis by proper clinical examination. Contact history of tuberculosis may be hidden by families to avoid the stigma associated with TB. Tests such as tuberculin sensitivity test and Interferon-Gamma Release Assays (IGRAs), if available, cannot distinguish definitively between TB infection and TB disease, and negative tests do not necessarily rule out TB. Chest X-rays (CXRs), when available, remain the primary imaging tool for paediatric pulmonary TB, particularly in high TB-burden countries, where access to more advanced imaging is limited. Although the radiological disease findings on CXR in children is wide, CXRs can serve as a critical component, when available, of the child TB diagnostic approach and can be used to support clinical decision-making [1].

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Due to the paucibacillary nature of pediatric TB, the next step of obtaining a good-quality specimen is another difficult task. However, microbiological confirmation should always be sought whenever possible, using available and recommended diagnostic tests and appropriate pediatric specimens, such as sputum, gastric aspirates, and stool and urine samples. Despite the best efforts and most advanced techniques, the microbiological positivity rate in detecting Mycobacterium tuberculosis (MTB) might not approach more than 30-40% [2]. It is only within this subset of pediatirc patients with positive microbiological tests that the concept of 'universal DST' can be applied (i.e., confirmation of resistance to at least rifampicin).

For children with DR TB, there is therefore another large subset of the population that will be diagnosed clinically and referred to as having "presumptive" or "probable"' DR TB. These children are those that will likely then be treated empirically for DR TB based upon clinical history and presentation, the results of other clinical and radiological testing, if available, and on a history of exposure to a close contact with a DR TB index case or poor response/failure to treatment with 1st line anti-tuberculosis drugs (i.e., isoniazid, rifampicin, pyrazinamide and ethambutol).

Due to the clinical and diagnostic challenges outlined, the annual figure of 30,000 new paediatric DR TB cases reported globally seems likely to be just the tip of the iceberg, while a large number of children remain undiagnosed and thereby not receiving the appropriate curative treatment [3].

In spite of the growing burden of multi-drug resistance and the challenges in diagnosing and treating children with DR TB, there have been significant advances in both the diagnostic and therapeutic modalities available to children with TB, offering some light at the end of the tunnel, in our fight against paediatric DR TB.

2. Molecular tests-The Game Changers in TB Diagnostics

There is no way to confirm drug resistance in TB through clinical precision and radiological methods. Therefore, clinicians should depend whenever possible on microbiological techniques; however, starting empiric DR TB treatment in a child should not be delayed while awaiting microbiological confirmation. Delay in diagnosis of drug resistance leads to improper treatment, clinical worsening for the child and also increased opportunity of transmission of TB. Liquid cultures have reduced the turnaround time (TAT) compared to the solid media cultures for isolating MTB to as early as two weeks and are the 'gold standard' for diagnosis. Yet, cultures are fraught with the disadvantage of the slow growth of Mycobacterium tuberculosis (MTB). Time is important in identifying the complete drug resistance mechanisms of the causative MTB pathogen as soon as possible to guide and tailor treatment decisions.

MTB has been identified with chromosomal mutations in the existing genes that are passed from mother to daughter cells that confer drug resistance. Examples of these resistance genes are for isoniazid (alterations in genes katG and inhA); rifampicin (in rpoB); streptomycin (in rrs and rpsL); pyrazinamide (in pncA); ethambutol (in embB); quinolones (in gyrA); and kanamycin (in rrs) [4]. Unlike other bacteria, these cells do not have plasmids and rarely exchange DNA laterally.

The following molecular diagnostics, which help in target amplification and gene sequencing of these known or suspected resistance genes, have been recently heralded as game changers for rapid diagnosis and initiation of appropriate treatment of DR TB:

2.1.1. Xpert MTB/RIF assay

Xpert MTB/RIF Assay is a fully automated nucleic acid amplification test and a cartridge-based assay which was approved for use by WHO in 2010. It provides for the diagnosis of MTB and rifampicin resistance in two hours.

2.1.2. Xpert Ultra (Cepheid Inc, Sunnyvale, CA, USA)

Xpert Ultra is an automated closed system and works on the same genexpert platform as Xpert MTB/RIF. The sensitivity of Xpert Ultra is higher than Xpert MTB/RIF due to its lower limit of detection -15.6 Colony forming Units /millilitre (CFU/ml) compared to 112.6 (CFU/ml) of Xpert

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MTB/RIF. It detects both live and dead MTB DNA. The melting temperature analysis in Xpert Ultra, instead of real-time PCR analysis with Xpert MTB/RIF, has also improved the detection of rifampicin resistance, especially in mixed infections, by the ability to differentiate between resistance-conferring mutations and silent mutations such as Q513Q and F514F[5]. However, its ability to detect very low MTB loads gives rise to trace positive reports and the inability to determine rifampicin resistance. Also, the specificity of Xpert Ultra is lower as it can detect non-viable bacteria in patients treated for TB in the near past.

2.1.3. Xpert MTB/XDR assay

This assay detects resistance to isoniazid, rifampicin, ethionamide, fluoroquinolones, and second-line injectables. Although the assay doesn't detect resistance to newer drugs such as bedaquiline (BDQ) and delamanid (DLM), it helps in the detection of 97% of current MDR TB in the adult population. Data on children is limited. However, its full utility may be diminished due to the recent move from injectable drugs to all oral TB drug regimens for eligible adults and children [6].

2.1.4. Line Probe Assays

MTBDRplus Line Probe Assay is used for the rapid diagnosis of MTB and resistance to RIF and INH. MTBDRplus can only detect mutations in rrs,eis genes, gyrA and gyrB genes, therefore additional phenotypic testing is required for a complete resistance profile.

2.1.5. Whole Genome Sequencing (WGS)

WGS provides DNA sequence data for the entire tuberculosis genome. It is a very promising tool as it overcomes the disadvantage of the limited number of known mutations that can be detected by molecular diagnostic tests. WGS helps in identifying resistance to newer TB drugs like BDQ, DLM, and linezolid and provides addition data to understand demonstrated phenotypic resistance. Also, the TAT for WGS is a few days compared to the several weeks required for drug susceptibility tests on MTB cultures. WGS is reported to have higher sensitivity and specificity in screening resistance for 1st line TB drugs than second-line drugs [7]. It can also help in differentiating new TB infection and disease and TB disease relapse, mapping the transmission network and tracing the source case. There are several challenges for WGS related to low DNA yield when sequencing directly from sputum, required expertise for analysis of large sequence data standardizations and cost. WGS data in the pediatric age group is sparse.

2.1.6. CRISPR-MTB

The Clustered Regularly Interspaced Short Palindromic Repeats assay (CRISPR) can work like molecular scissors on MTB and is a promising tool being evaluated in children as it can detect MTB directly from all bodily fluids with great sensitivity. An expanded CRISP-MTB assay can also help in detecting resistance to TB drugs [8].

2.2. Application of molecular tests with improved diagnostic approaches in children

2.2.1. Induced sputum

Induced sputum is a non-invasive method of sputum collection with a microbiological yield similar to three sequential gastric lavages [9].

The sensitivity of Xpert MTB/RIF on induced sputum in children is about 66% with a specificity of 98% in comparison to culture [10]. A Cochrane review of Xpert MTB/RIF in children found the highest sensitivity for sputum, followed by gastric aspirate and stool and lowest sensitivity with nasopharyngeal aspirate [11].

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2.2.2. Stool

MTB bacilli are known to be shed in the stools after overnight swallowing of sputum containing MTB. The feasibility of stool testing methods provides convenience for non-invasive specimen collection, especially in children younger than five years, who currently often require more invasive TB diagnostic methods. The pooled sensitivity of Xpert MTB/RIF testing in stool specimens was higher in children with HIV as compared to children uninfected with HIV in two independent systematic reviews and meta-analyses which analysed the diagnostic accuracy of Xpert testing of stool specimens for diagnosis of pulmonary TB [12,13]. The authors noted the limitations of the lack of age-specific data on performance, especially for the younger age groups, as well as the wide variability of stool preparation and testing protocols.

In comparison with Xpert MTB/RIF, Xpert Ultra testing on stool specimens had higher sensitivity and lower specificity [14]. The higher sensitivity was attributed to the low limit of detection and ability to detect trace positive results. The current methods used for processing stool specimens for such tests are relatively resource intensive. Due to the high percentage of trace positive results in Xpert Ultra, further comparative evaluation is required for diagnostic accuracy in children with and without trace positive results.

WHO guidance has recommended stool specimens alongside specimens like sputum, nasopharyngeal aspirate or gastric aspirate using either Xpert MTB/RIF and Xpert Ultra for diagnosis of pulmonary TB in children under 10 years of age since 2021 [15]. A practical manual for processing stool samples was released in 2022 to standardise the testing methodology of stool specimens for TB testing tuberculosis [16].

2.2.3. Tissue biopsy and CSF

Children have a higher proportion of extra-pulmonary TB compared to adults. Xpert MTB/RIF utilized to test lymph node (LN) tissue or LN aspirates and the cerebrospinal fluid have lower sensitivity of 80% and 42% respectively, despite high specificity of over 90% [12]. In a pediatric study of 55 cases of TB meningitis , the Xpert MTB/RIF assay demonstrated a sensitivity and specificity of 40% and 92.5% respectively and a 78.2% diagnostic accuracy compared to culture [17].

2.2.4. Combination of two or more specimens for molecular testing methods

Duplication of nasopharyngeal aspirate or one nasopharyngeal aspirate plus one stool specimen is reported to produce a good microbiological yield by smear/culture with sensitivity above 70% in young children and equivalent to the yield of two samples of gastric aspirate [18,19].

3. New Players in TB Therapeutics in Children

The pharmacokinetic data of the anti-tuberculosis drugs in children is limited and most of the doses used in the current regimens are extrapolated from weight-based adult doses. The restricted availability of pediatric-friendly drug formulations also creates issues with compliance [20].

Delayed diagnosis, limited psychosocial and nutritional support, incomplete monitoring of adverse events, and incomplete coordination with other programmes such as HIV, nutrition, as well as untrained staff, are common problems that are faced by resource-limited settings.

Therefore it is no surprise that there is a striking difference in the pooled treatment success of MDR TB with the present recommended regimens among children belonging to LMI countries (73%) in comparison to those in developed nations (87%) [21].

3.4.1. Clinical Pharmacological studies in children

Due to the age-related changes in pharmacokinetic and pharmacodynamic (PK/PD) parameters in children, the pediatric doses derived from extrapolation from adults are inappropriate [22]. PK/PD studies will help to identify the dosing regimen that can safely expose children to the therapeutic drug levels that adults achieve with their standard recommended doses [22] Also, there is a paucity of prospective studies on the adverse effects of TB medicines in children. Adverse effects

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such as hearing and vision impairment or neuropathy might be underreported due to the difficulty in diagnosing these impairments without specialized tests. MDRPK1 and MDRPK2 studies were conducted to close the knowledge gaps for PK and safety data for Levofloxacin, Moxifloxacin and Linezolid in young children[23–25]. Moxifloxacin doses need to be increased above the currently recommended 10-15 mg/kg/day in young children to be equivalent to the therapeutic adult doses, however safety issues have not been evaluated especially when co-administered with other drugs which prolong QT interval [25].

Novel drug formulations of second-line drugs , such as dispersible tablets for bedaquiline, delaminid, pretomanid and gummy formulations for moxifloxacin and clofazamine are being developed for better palatability and acceptance [22].

3.4.2. New and repurposed drugs

In March 2022, the WHO recommended the use of BDQ and DLM in children of all age groups, for treatment of drug-resistant TB [26], and in 2023 they also released 2 information notes to provide practical information and guidance for implementation of novel formulations of bedaquiline and delamanid in line with recommendations for their use in children of all ages [27,28]. These new and repurposed drugs have brought promising opportunities to shorten the otherwise long duration of treatment and to move away with injectable drugs and drugs with severe adverse effects and drug interactions.

3.4.2.1. Delamanid (DLM)

DLM inhibits the synthesis of methoxy- and keto-mycolic acid present in the cell wall of MTB while generating nitrous oxide. It has an oral bioavailability of up to 47%, and peaks at around 4–8 h after oral dosing with a half-life of 30–38 hours. A steady-state concentration is reached after about 2 weeks [29]. DLM is generally well tolerated. However, due to its potential adverse effect of prolongation of QT interval, clinicians are advised to monitor for cardiac safety with ECG and serum electrolytes and also to avoid other drugs which can prolong the QT interval. Several ongoing trials evaluating the safety of DLM in children (including NCT01859923, NCT01856634, and NCT03141060) are in the early phase of clinical trials.

Based on the growing evidence of efficacy at the time of making the recommendation, WHO lowered the age recommendation of DLM from above 6 years in 2016 to include 3 to 6 years of age in 2019 and subsequently to all ages for inclusion into longer duration treatment regimens [26]. It should be noted that the adult formulation (50 mg) of delamanid is not to be split or crushed for dosing in paediatrics as the bioavailability can be compromised; therefore, the 25 mg dispersible formulation needs to be used in children.

3.4.2.2. Bedaquiline(BDQ)

BDQ inhibits the mycobacterial ATP synthase proton pump. It reaches peak concentration in 5-6 hours and has a half-life of more than 24 hours. BDQ is usually well tolerated with common side effects of nausea, headache, and arthralgia. It can cause prolongation of QT interval (especially after 18 weeks of use) and therefore should be used with caution with delamanid, clofazimine and fluoroquinolones which have similar adverse effects. It should be noted that its efficacy can be reduced when co-administered with CYP3A inducers like rifampicin, while its toxicity can be increased when administered with ketoconazole or lopinavir/ritonavir [30].

Interim reports were available with WHO, from ongoing paediatric trials on BDQ, namely TMC207-C211 in children aged 5-18 years and IMPAACT P1108 in children aged 0-6 years in 2022, which did not note any higher adverse effects in the paediatric age group in comparison to the adults [26,31] , [see Tables 1–3]. After extrapolating the data on efficacy from the adult population, WHO stated that:

“A shorter all-oral bedaquiline-containing regimen of 9-12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/ RR-TB) who

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have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded."

A mutant atpE gene can confer resistance to BDQ. Currently, there is no standard way of testing for BDQ resistance [32].

Currently recommended regimens by WHO for DR TB treatment in children are summarised in Table 1.

In children with rifampicin sensitive and isoniazid resistant TB, treating with rifampicin, ethambutol, pyrazinamide and levofloxacin for 6 months is recommended. In the children eligible for the 9 month all-oral drug regimen, bedaquiline is given for 6 months with a combination of levofloxacin/moxifloxacin, ethionamide, ethambutol, high dose isoniazid, pyrazinamide and clofazimine for at least 4 months , with extension to 6 months in case of sputum positivity at 4 months. This is followed by a 5-month regimen of levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide for 5 months duration [26].

For children who do not meet the eligibility criteria for the standardised all-oral bedaquiline regimen, it is recommended to provide longer and individualised treatment regimens containing bedaquiline and at least four medicines to which the organism is susceptibile. Priority needs to be given to Group A and Group B medicines in determining the regimen with the addition of Group C drugs based on the assessment of risks and benefits [26].

Table 1. Current Regimens Recommended by WHO for DR TB Treatment in Children [26].

Regimens	Regimen	Eligibility
Isoniazid Monoresistance	6 month regimen of (H)REZ-Lfx . In case Lfx cannot be used, (H)REZ to be given for 6 months. No need to add streptomycin.	For children of any age with Isoniazid mono-resistance.
Shorter all oral 9 months regimen for MDR/RR-TB	4–6 months regimen of $Bdq_{(6\ months)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 month regimen of Lfx/Mfx-Cfz-Z-E	• MDR/RR TB Fluoroquinolone resistance excluded • Not exposed to 2nd line TB medicines for more than one month • No extensive TB disease+ • No severe extrapulmonary TB&
Shorter regimen for MDR/RR-TB with Quinolone resistance	6–9 month treatment regimen composed of bedaquiline, pretomanid and linezolid – **BPaL regimen***	• Bacterio logically confirmed **Pulmonary TB** • Age at least 14 years of age and weight greater than 35 kg • Not pregnant/breastfeeding and willing to use effective contraception • No known allergy/known resistance to any components of regimen

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		• Not exposed to components for more than 2 weeks • No extra-pulmonary TB **Relative contradindications:** • Concurrent use of medications that can have drug interaction with BPaL component drugs • High risk of cardiac arrhythmia • Severe anemia, leucopenia or thrombocytopenia • severe hepatic failure • severe renal failure • severe neuropathy
Longer regimen for MDR/RR-TB	18 months regimen $Bdq_{(6\ m)}$-Lfx/Mfx-Lzd-Cfz	For those not eligible for shorter all oral Bedaquiline containing MDR TB regimen

*Moxifloxacin can be added to this regimen (BPaLM) in case there is absence or unknown resistance to fluoroquinolones. H Isoniazid, Hh High dose Isoniazid, R Rifampicin, E Ethambutol, Z Pyrazinamide, Lfx Levofloxacin, Bdq Bedaquiline, Mfx Moxifloxacin, Cfz Clofazamine, Eto Ethionamide, Pa pretomanid. +Extensive TB disease is defined in this document as the presence of bilateral cavitary disease, or extensive parenchymal damage on chest radiography. In children aged under 15 years, the advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. + Severe extra-pulmonary TB is defined as the presence of miliary TB or TB meningitis. In children aged under 15 years, extra-pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe.

Table 2. Regimen for Bedaquiline, Pretomanid and Linezolid (BPaL) for ages ≥ 14 years* [26].

Antitubercular drug	Dose
Bedaquiline	400 mg OD x 2 weeks , then 200 mg 3 times per week
Pretomanid	200 mg OD
Linezolid	1200 mg OD (dose can be reduced in case of linezolid induced neuropathy)

*Treatment duration is 6-9 months.

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Table 3. Drug doses and side effects for second-line drugs based on estimated therapeutic efficacy (adapted from WHO recommendations) [26].

Drug	Dosage	Major Side-effect
Levofloxacin	15-20 mg/kg	QT prolongation, psychiatric disturbance
Moxifloxacin	10-15 mg/kg *10 mg/kg in less than 6 months*	QT prolongation, psychiatric disturbance
Bedaquiline	**For 100 mg tablet:** (100 mg in 10 ml =10 mg/mL) *0 to <3 months:* 3 ml OD for 2 weeks; then 1 ml OD M/W/F for 22 weeks *≥3 to <6 months (3 to <10 kg):* 6 ml OD for 2 weeks; then 2 ml OD M/W/F for 22 weeks *≥ 6 months (10 to <16 kg):* 8 mL OD for 2 weeks; then 4 mL OD M/W/F for 22 weeks *16-30 kg:* 2 tab OD x2 weeks then 1 tab OD M/W/F for 22 weeks *30 to <46 kg:* 4 tab OD x2 weeks then 2 tablet OF M/W/F for 22 weeks **For 20 mg Dispersible tablet:** *0 to <3 months:* 1.5 OD for 2 weeks; then 0.5 OD M/W/F for 22 weeks *≥ 3 to <6 months:* 3 OD for 2 weeks; then 1 OD M/W/F for 22 weeks *≥ 6 months (7 to 10 kg):* 4 OD for 2 weeks; then 2 OD M/W/F for 22 weeks *≥ 6 months (10 to <16 kg):* 6 OD for 2 weeks; then 3 OD M/W/F for 22 weeks *16-29 kg:* 10 OD for 2 weeks then 5 tablet OD M/W/F x 22 weeks. *>29 kg:* 20 OD x 2 weeks then 10 DTS M/W/F x 22 weeks.	Drug interactions with drugs that inhibit or induce cytochrome P450 enzymes, QT prolongation
Linezolid	For 1-15 kg 15mg/kg OD ; For >15 mg/kg 10-12 mg/kg OD	Bone marrow suppression, peripheral neuropathy, optic neuritis, Gastrointestinal disorders
Clofazamine	2-5 mg/kg *(give on alternate days if daily dose is very high)*	Can prolong QT when used with drugs that prolong QT

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		like BDQ, DLM and fluoroquinolones. orange discolouration of skin, conjunctiva, cornea and body fluids; dry skin, pruritus, rash, ichthyosis and xerosis; gastrointestinal intolerance; and photosensitivity. Dose adjustment needed in severe hepatic insufficiency.
Cycloserine	15-20 mg/kg	inability to concentrate and lethargy seizure, depression, psychosis and suicidal ideation, peripheral neuropathy, lichenoid eruptions and Stevens-Johnson syndrome.
Ethambutol	15-25 mg/kg	Ophthalmic, GI disturbance
Delamanid	*<3 months:* 25 mg OD *≥3 months :* *<16 kg :* 25 mg BD; *16 kg to <30 kg :* 50 mg morning and 25 mg evening; *>30 kg:* 50 mg BD *12-17 years:*100 mg BD	Nausea and Vomiting, QT prolongation, Hallucinations, paraesthesia
Pyrazinamide	30-40 mg/kg	Hepatotoxicity, arthralgia, GI disturbance, dermatological disorder
Meropenem	20-40 mg/kg/IV every 8 hourly (to be used with Clavulinic acid)	GI disturbances, Seizures, hepatic and renal dysfunction
Amikacin	15-20 mg/kg/day (Max 1 g/day)	Nephrotoxicity, ototoxicity
Streptomycin	20-40 mg/kg (Max 1 g/day)	Ototoxicity
Ethionamide or prothionamide	15-20 mg/kg (Max 1 g/day)	Hypothyroidism
P-amino salicylic acid	200-300 mg/kg in 2 divided doses	Hypothyroidism, GI disturbance
Isoniazid	15-20 mg/kg/dose *(To be given with pyridoxine)*	Peripheral neuropathy

4. Prevention of TB and DR TB:

As per mathematical modelling, three in every 1000 people carry latent DR TB and children below 15 years of age have double the prevalence of latent TB [33]. There are limited observational studies involving preventive therapy in children who are in contact with MDR household members.

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4.1. TB Preventive Therapy (TPT):

There are currently several ongoing trials for MDR TB preventive therapy in children. TheV-QUIN Phase III in Vietnam and TB CHAMP Phase III in South Africa are evaluating the efficacy of levofloxacin versus placebo as TPT. The PHOENix Phase III is comparing the efficacy of delaminid versus isoniazid as part of an international multi-centre trial. All three trials are evaluating TPT treatments of 6 months duration with follow-up for up to 2 years [34]. It was found in the lead-in study to the TB CHAMP trial that though the novel dispersible tablet of 100 mg levofloxacin was acceptable, there remained the challenges of a psychosocial burden on caregivers for providing effective preventive therapy to children [35]. Studies are lacking on fluoroquinolone-resistant MDR TB contacts [35]. Current WHO guidelines recommend that preventive therapy can be considered for children in contact with patients with MDR-TB based on individualized risk assessment and sound clinical justification [36].

4.2. TB Vaccines:

In the year 2021, the Bacillus Calmette–Guérin vaccine (BCG) celebrated" its 100th anniversary. The WHO s Expanded Program on Immunization (EPI) has included BCG since 1976 and to date more than 4 billion people have received the vaccine, the majority children. BCG is a part of the national immunization schedule in 154 countries, given to newborns, with coverage rates of >85% [37]. However, protection from BCG has its limits. BCG confers 60–80% protective efficacy against severe forms of tuberculosis (including TB meningitis and miliary TB) in children, it may prevent approximately 20% of children from developing TB infection, and of those infected, it is likely to protect 50% from developing active TB disease. The protection for adolescents and adults has until recently, reported to be minimal [38]. BCG was found to be highly effective in absence of prior MTB or sensitisation of mycobacteria from the environment [39].

Preferred Product Characteristics (PPC) for the various TB vaccination approaches, such as those for improving the current TB vaccinations in infants aiming at safer and more effective vaccines than BCG have been developed by the WHO. Likewise, vaccines for adolescents and adults who may or may not be already infected with MTB are underway. The vaccine likely to have the most substantial impact on the TB epidemic is one which can be given to adults and adolescents to prevent TB disease and thereby decrease its community transmission.

The TB vaccine pipeline includes whole-cell vaccines, recombinant subunit vector vaccines, and adjuvant proteins among the 14 candidates currently in clinical development (phase 1 and beyond) [40,41]. Candidate vaccines are being investigated for their role in the prevention of disease (POD), prevention of infection (POI), and prevention of recurrence (POR).

At present three candidates are in phase 3 development: VPM1002, MIP and MTBVAC**.** VPM1002 and MIP are in a phase 3 trial to evaluate their efficacy and safety for POD among healthy household contacts (HHC) > 6 years of age, of newly diagnosed sputum-positive pulmonary TB patients [42]. VPM1002 is also being evaluated in a phase 3 study for POI among newborns [43]. MTBVAC which is being evaluated for POD among infants, is already in phase 3 development [44].

A POI vaccine, which can be given at birth, could be the ideal candidate as protection would be conferred earlier and fewer vaccines are given in adolescence. However, given the potential impact a POD vaccine can have if given to older children, adolescents, and adults in population-based campaigns under programmatic settings, it is being funded and supported as an initial TB vaccine rollout candidate. Vaccines providing both POD and POI offer a combined approach of not only protecting infants from birth but also protecting older children and adolescents from developing TB disease if they have already been exposed to TB.

5. Challenges and the way forward

It is encouraging to note that children with XDR TB have had much more favourable outcomes in comparison with adults [45]. Every effort needs to be made to ensure that each child gets the appropriate management customised to the pathogen resistance pattern, while minimizing adverse events. Decentralisation of TB services are recommended through family-centred integrated care services at the peripheral levels of the health system while continuing with specialised pediatric TB services at higher levels of the health system [36]. Capacity building for prompt diagnosis and treatment, continuous training of health care staff, ensurance of regular supplies of TB medicines, monitoring for adverse effects and compliance and additional support systems for nutrition and psychological support, coupled with attention to contact tracing and abolishing the stigma associated with TB, is crucial for the successful outcome of DR TB treatment.

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