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SUPPLEMENT ARTICLE

New Drugs and Regimens for Tuberculosis Disease Treatment in Children and Adolescents

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After almost 30 years of relative stagnation, research over the past decade has led to remarkable advances in the treatment of both drug-susceptible (DS) and drug-resistant (DR) tuberculosis (TB) disease in children and adolescents. Compared with the previous standard therapy of at least 6 months, 2 new regimens lasting for only 4 months for the treatment of DS-TB have been studied and are recommended by the World Health Organization (WHO), along with a shortened 6-month regimen for treatment of DS-TB meningitis. In addition, the 18- to 24-month regimens previously used for DR-TB that included painful injectable drugs with high rates of adverse effects have been replaced with shorter, safer all-oral regimens. Advances that have improved treatment include development of new TB drugs (bedaquiline, delamanid, pretomanid), reapplication of older TB drugs (rifampicin and rifapentine), and repurposing of other drugs (clofazimine and linezolid). The development of child-friendly formulations for many of these drugs has further enhanced the ability to safely and effectively treat DS- and DR-TB in children and adolescents. The characteristics and use of these drugs, regimens, and formulations are reviewed.

Key words: child-friendly formulations; children and adolescents; multidrug/rifampicin-resistant; pharmacokinetics; tuberculosis.

Of the 1.2 million children <15 years of age estimated to develop tuberculosis (TB) disease each year, only about a third are diagnosed and treated [1, 2]. Even worse, of the 30 000 children estimated to have multidrug-resistant (MDR) TB [3] (disease caused by an organism resistant to at least isoniazid and rifampicin) only about 5000 are treated annually [1, 4].

While outcomes for children who are diagnosed and appropriately treated for drug-susceptible (DS) and MDR-TB are generally good, there are several reasons why even better treatment regimens would be beneficial [5, 6]. First, treatment outcomes continue to be suboptimal for children living with human immunodeficiency virus (HIV) and other immunocompromising conditions [7]. Second, the greatest cause of TB-related mortality in children continues to be TB meningitis (TBM), and unfortunately, when new drugs are approved for TB use, limited data about central nervous system penetration are usually available. The improvements in treating pulmonary TB have not yet affected the treatment of TBM. Third, treatment regimens remain long compared with most infectious diseases, leading to adherence issues and increased costs for families and the health system. Fourth, some of the drugs still used to treat children for TBM and MDR-TB in some parts of the world commonly cause adverse effects, especially the injectable drugs (aminoglycosides and capreomycin), which cause hearing loss in a substantial proportion of treated children [8]. In low-income settings, these drugs are commonly given intramuscularly, causing pain and anxiety for children. Fifth, before the development of dispersible formulations, many of the drugs used for MDR-TB were difficult to use in small children. Finally, many clinicians in high-burden areas have been reticent to treat children for TB disease based solely on clinical grounds. If shorter durations of treatment, lower rates of drug toxicity, and improvements in drug acceptability were accomplished, clinicians would likely start treatment at an earlier stage and in more children without requiring confirmation of disease.

Following years of neglect [9], the last decade has seen dramatic progress in TB therapeutics with new drugs and regimens being evaluated in adults and, increasingly, studies are also being carried out in children. In 2022, the World Health Organization (WHO) revised its guidance on the management of TB in children and adolescents, which included important new recommendations for the treatment of DS- and MDR-TB (Table 1). In this review, we outline the most recent developments in child and adolescent TB disease therapeutics.

PEDIATRIC DRUG DEVELOPMENT

The challenges inherent in pediatric drug development include study recruitment and ethical considerations; the need

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Table 1. Summary of Updated World Health Organization (2021-2022) Recommendations for the Treatment of Tuberculosis (TB) in Children

New Recommendation	Comments
Drug-resistant TB treatment	
1. In children with MDR/RR-TB of all ages, bedaquiline may be used as part of the shorter, all-oral bedaquiline-containing regimen (conditionally recommended by WHO in 2020) or as part of the longer treatment regimen	Interim bedaquiline dosing guidance for all ages to be shared by WHO in an operational handbook to support this recommendation
2. In children with MDR/RR-TB of all ages, delamanid may be used as part of the longer treatment regimen	Interim delamanid dosing guidance for all ages to be shared by WHO in an operational handbook to support this recommendation
Drug-susceptible TB treatment	
3. In children and adolescents under 16 years of age with non-severe, presumed drug-susceptible TB, a 4-month regimen (2HRZ(E)/2HR) should be used rather than the standard 6-month regimen (2HRZ(E)/4HR)	Important implementation considerations, especially how to determine eligibility (non-severe disease), to be shared by WHO in an operational handbook and in the newly launched chest radiology Atlas
4. A 4-month rifapentine containing regimen (8 weeks of HPZM followed by 9 weeks of 2HPM) may be used as an alternative for the treatment of pulmonary drug-susceptible TB in adolescents 12 years of age and older	May be used for severe and non-severe pulmonary TB. The dose of rifapentine is 1200 mg daily
TB meningitis treatment	
5. In children and adolescents with microbiologically confirmed or clinically diagnosed TB meningitis, presumed to be drug-susceptible, a 6-month intensive regimen composed of 6HRZE to may be used as an alternative option to the WHO-recommended 12-month regimen composed of 2HRZE/10HR	The existing recommendation for the 12-month regimen composed of 2HRZE/10HR remains in place. New dosing guidance for rifampicin for TB meningitis treatment to be shared by WHO in an operational handbook

Abbreviations: TB, tuberculosis; MDR/RR, multidrug-resistant/rifampicin-resistant; WHO, World Health Organization; R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; P, rifapentine; M, moxifloxacin; Eto, ethionamide.

for improvements in study design; insufficient trial site infrastructure; the absence of community involvement; and lack of investments [10, 11]. Many regulators, including the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA), have requirements and incentives to develop pediatric formulations following regulatory approval of innovative adult medicines. Still, the availability of pediatric TB formulations has lagged approximately 7 years behind that of adult formulations for both bedaquiline and delamanid and innovative approaches will be needed to accelerate pediatric TB drug development. Despite these challenges, developments in the use of new drugs, repurposed drugs, and new applications of old drugs for child TB have taken place in recent years (Table 2).

NEWER TB DRUGS

Bedaquiline

Bedaquiline is a diarylquinoline that blocks mycobacterial ATP synthase [12, 13]. The primary safety concerns are QT interval prolongation, hepatotoxicity, and arthralgia, although it is generally safe and well tolerated [14]. Since its accelerated approval by the US FDA in 2012 [15], it has been shown to reduce the risk of mortality or unsuccessful outcome in adults with MDR-TB [16, 17]. It is now recommended by the WHO for the treatment of rifampicin-resistant (RR) TB in an all-oral shortened regimen, and to be included as a priority in individually constructed regimens [18]. It is part of the 6-month BPaL regimen (bedaquiline, pretomanid, linezolid) studied in Nix-TB [19], in which 109 adults with either extensively drug-resistant TB (XDR-TB) or intolerance to second-line drugs for MDR/RR-TB, were treated with BPaL for 6 months. While this regimen was found to be highly efficacious, frequent toxicities primarily due to linezolid have been seen. The most recent WHO guidance advised this regimen can be used for the treatment of RR-TB with additional fluoroquinolone resistance. In addition to use in the BPaL regimen, bedaquiline is also a component of multiple shortened regimens being evaluated in adults [20].

Pediatric studies of bedaquiline, to characterize its pharmacokinetics (PK), dose and safety in children, were delayed. The Janssen-sponsored phase I/II C211 study (NCT02354014) is an age de-escalation trial that opened in 2016, 4 years after bedaquiline's approval for adults. Study of the first 2 age cohorts (12 to <18 years, 5 to <12 years) led to the approval of a 20 mg dispersible tablet formulation and extension of the FDA approval down to age 5 years and 15 kg body weight in 2020 [21, 22]. As of early 2022, the third cohort (2 to <5 years) is ongoing, and the youngest cohort (0 to <2 years) will only open after that is complete. The IMPAACT P1108 phase I/II trial is a modified age de-escalation trial that opened in 2017, and as of early 2022 is enrolling across all age cohorts (0 to <18 years) [23]. Data review from these 2 trials led WHO to recommend bedaquiline for children of all ages with RR-TB with preliminary dosing recommendations for children down to birth (https://www.who.int/publications/i/item/9789240046832) [24, 25]. Key remaining priorities for bedaquiline in children include completing the above trials to inform definitive dosing recommendations, and confirming pediatric doses for a simplified, daily bedaquiline dosing approach being increasingly utilized in adults [26].

Delamanid

Delamanid is a nitroimidazole antibiotic with activity against *M. tuberculosis* due to inhibition of mycolic acid synthesis

Table 2. New, Repurposed, and Older TB Drugs With New Uses

	Current Pediatric Data	Key Pediatric Knowledge Gaps	Ongoing or Planned Pediatric Trials, as of Early 2022
Bedaquiline	PK, dose, safety data in children ≥6 years of age Preliminary PK, dose safety in children <6 years of age	Confirm PK, dose, safety in children <6 years of age PK, dose, safety of simplified daily dosing regimen being evaluated in adults (200 mg daily × 2 weeks, 100 mg daily thereafter)	Janssen C211, phase I/II trial of bedaquiline PK, safety in children with MDR-TB; cohort 3 (2 to <5 years of age) ongoing; cohort 4 (<2 years of age) not yet open IMPAACT P1108, phase I/II trial of bedaquiline PK, safety in children with MDR-TB; open to all ages (0-17 years) No current study planned to confirm simplified dosing approach in children treated for RR-TB
Delamanid	PK, dose, safety data in children ≥10 kg body weight Preliminary dose in children <10 kg body weight, based on modeling and simulations	Confirm PK, dose, safety in children <10 kg body weight PK, dose, safety of simplified once-daily dosing regimen being evaluated in adults	IMPAACT 2005, phase I/II trial of PK, safety of optimized doses of delamanid in children 0-17 years of age with RR-TB; open to all ages PHOENIx lead-in pediatric PK study of once-daily delamanid in children with household MDR-TB exposure; open No current study planned to confirm once-daily dosing approach in children being treated for RR-TB disease
Pretomanid	None	PK, dose, safety in children with RR-TB	IMPAACT 2034, phase I trial of PK, safety of a single dose of pretomanid in children with RR-TB; in development, to open in 2022 Multiple-dose phase II trial to follow on the single-dose study
Clofazimine	Limited PK, safety data, primarily from non-TB cohorts	PK, dose, safety in children with RR-TB	Clofazimine Kids, phase I/II trial of PK, safety of clofazimine 50 mg gel caps (Novartis) in children with RR-TB; open to all ages (0-17 years); open to all ages CATALYST trial, phase I/II trial of PK, safety of clofazimine 50 mg tablets (Macleods) in children with RR-TB; open to all ages (0-17 years); open to all ages
Linezolid	PK, dose, safety data from small, observational PK studies for children across all ages	Confirmatory PK, safety data in children with RR-TB Data on optimal duration of linezolid for RR-TB treatment in children	None
Rifampicin	PK, dose, short-term safety of doses approximating an adult 35 mg/kg dose	Confirmatory PK data, safety and tolerability data for longer use (8 weeks or longer) Potential of high-dose rifampicin to shorten treatment in children with drug-susceptible TB PK, safety, efficacy of higher doses of rifampicin for children with TB meningitis	HighRIF-C, a phase I/II trial of the PK, safety and tolerability of 30 mg/kg and 40 mg/kg in children with DS-TB; open SURE, a phase III trial of a short intensive regimen for children with TB meningitis, including rifampicin 30 mg/kg; open
Rifapentine	PK, dose, safety of rifapentine in 3HP regimen for children ≥2 years of age	PK, dose, safety of rifapentine in 3HP regimen for children <2 years of age PK, dose safety of rifapentine in 1HP regimen for children 0-17 years of age PK, dose, safety of rifapentine in 2HPMZ/2HPM regimen in children 0-17 years of age	Study 35, a phase I/II trial of the PK, safety of rifapentine and isoniazid administered weekly for12 weeks (3HP) in children up to 12 years of age with latent TB infection; open to all ages IMPAACT 2025, a phase I/II trial of the PK/safety of daily rifapentine and isoniazid for 1 month (1HP) in children with latent TB infection; in development RADIANT Kids, a phase I/II trial of PK, safety of rifapentine and moxifloxacin in the 2HPMZ/2HPM regimen in children with DS-TB; in development

Abbreviations: PK, pharmacokinetics; TB, tuberculosis; RR, rifampicin-resistant; MDR, multidrug-resistant; DS: drug-susceptible.

[27, 28]. It has a good safety profile, with QT prolongation the primary safety concern [28]. Delamanid received conditional approval from the EMA in 2014 based on phase II trial data in adults with MDR-TB, but disappointing phase III trial results raised questions about its optimal use [29]. Its most common use currently is when there is resistance or intolerance to other drugs with its definitive role still to be defined through ongoing trials [20]. Delamanid is available in the United States only through compassionate use.

The Otsuka-sponsored pediatric trials, completed in 2020, studied the PK and safety of delamanid over 10 days in a phase I trial and over 6 months in a phase II extension trial. Delamanid was reported to have minimal QT prolongation and no unexpected safety signals [30]. The doses studied met PK targets in the older cohorts (2 to <18 years) but were far below targets in children <2 years [30]. Based on these data, in 2021, the EMA approved a 25 mg dispersible tablet and use down to 10 kg of body weight [28]. The WHO-recommended delamanid for use in children with RR-TB down to age 6 years in 2016, down to age 3 years in 2019, and for children of all ages in 2021 [24, 31]. Preliminary dosing recommendations for children <10 kg based on modeling and simulation were provided by the WHO in 2022 [32]. The IMPAACT 2005 trial (NCT03141060) will confirm the optimal dose of delamanid in children <10 kg where

there remains uncertainty. A lead-in pediatric PK study to the PHOENIx trial (NCT03568383), to treat presumed MDR-TB infection without disease, is studying once-daily delamanid dosing in children.

Pretomanid

Pretomanid is a nitroimidazooxazine antimicrobial similar to delamanid. Its approval is unusual as it has been approved only as part of a specific drug regimen. It received FDA approval in 2019 for adults based on the results of the Nix-TB trial and is a component of multiple regimens currently under evaluation in adults [20]. The PRACTECAL trial showed that a 6-month regimen of BPaL and moxifloxacin (BPaLM) was favored to the standard of care control arm (locally accepted standard of care consistent with WHO recommendations for the treatment of M/XDR-TB), adding to the evidence base for pretomanid [19, 20].

Pretomanid evaluation in children has been very delayed, in part due to safety concerns for testicular atrophy and impaired fertility seen in male rats [33]. Adult clinical studies have not identified this adverse effect; however, a study to definitively rule out this safety concern in humans is underway (NCT04179500) with results expected in 2023 [23]. The PK of a single dose of pretomanid in children will be studied in the phase I trial IMPAACT 2034, which is expected to open in mid-2022. Following this single-dose study and successful completion of the definitive male reproductive toxicity study, a multiple-dose pediatric trial will be needed before pretomanid can be used in children.

REPURPOSED TB DRUGS

Clofazimine

Clofazimine is a riminophenazine used traditionally for leprosy that has now been repurposed for TB treatment [34]. The primary safety concerns are QT interval prolongation, reversible skin discoloration, and gastrointestinal complaints [35, 36]. Evidence for its role in MDR-TB treatment comes primarily from several observational studies and the STREAM trial that showed the effectiveness of a shortened regimen (9-11 months) that included clofazimine [37, 38]. It is recommended by the WHO as a part of the shortened, all-oral regimen for MDR/RR-TB, and is a component of multiple shortened regimens under evaluation in adults [20, 24].

Although clofazimine has been used for leprosy treatment in children, there are limited pediatric PK data [39]. Dosing has been difficult with the soft gel capsules which are difficult to break up; dosing often had to be based on the total weekly dose divided by the number of milligrams in the tablet, resulting in the number of days a week the medicine should be given. Two pediatric phase I/II trials in children with RR-TB are underway: the Clofazimine PK trial opened in 2020 and is studying clofazimine 50 mg soft gel caps (Novartis); the CATALYST trial (PACTR202012756409365) opened in 2021 and is studying clofazimine 50 mg tablets (Macleods) in a more child-friendly formulation. Results of both trials are expected in 2023.

Linezolid

Linezolid is an oxazolidinone antimicrobial historically used for the treatment of Gram-positive infections that has been repurposed for the treatment of drug-resistant (DR)-TB. Multiple studies, including the Nix-TB trial, have confirmed its excellent efficacy against TB [19, 20, 40]. Its major limitation is frequent, often severe, dose- and duration-dependent adverse events, including peripheral neuropathy, anemia, thrombocytopenia, neutropenia, and less frequently, lactic acidosis and optic neuropathy [19, 41]. However, giving smaller daily doses, once-daily dosing, and shorter durations of therapy have reduced the rates of adverse effects without reducing effectiveness [20, 42] Linezolid is now a priority agent for individually constructed regimens [18, 24].

There are extensive pediatric PK data for linezolid when treating acute bacterial infections, but data for children treated for TB are limited. Current WHO dosing recommendations are based on observational PK studies in children treated for RR-TB [43]. In these studies, 10 of the 17 (59%) children treated long term with linezolid experienced a linezolid-related event, with anemia being the most common (n = 10). Five of these events were grade 3 or higher and occurred at a median time of 2.4 months, so careful monitoring, especially of hemoglobin, is important from the beginning of treatment. Safety will be improved by limiting the duration of linezolid treatment when possible; the optimal duration remains to be defined.

NEW APPLICATIONS OF OLDER TB DRUGS

Rifampicin (Rifampicin in Some Countries)

A renewed interest in optimizing the dose of rifampicin has led to a resurgence of research on this older TB drug [44]. A series of trials have shown that oral rifampicin doses of up to 40-45 mg/kg daily are safe and well tolerated by adults with TB, result in higher than proportional exposures, and lead to increased bactericidal activity and more rapid sputum culture conversion [45]. High rifampicin doses are being evaluated in adults in phase III trials for the potential to shorten treatment for DS-TB (RIFASHORT, NCT02581527; TRUNCATE-TB, NCT03474198), and for the potential to improve outcomes in TBM (HARVEST study, ISRCTN15668391). The Opti-Rif trial evaluated escalating doses of rifampicin in children with DS-TB to identify pediatric doses approximating exposures in adults receiving 35 mg/kg [46]. Oral doses of 65-70 mg/kg were required to reach these targets, and up to 60 mg/kg doses were

safe and well tolerated over 2 weeks. The HighRIF-C trial is evaluating 30 and 40 mg/kg doses in children (NCT04437836). Follow-up studies should evaluate the safety and tolerability of these higher doses over longer durations and explore their potential to shorten DS-TB treatment and improve outcomes in TBM. Rifampicin exposures with currently recommended doses in children with TBM are below target exposures, and 2022 WHO recommendations call for rifampicin doses of 22-30 mg/kg for TBM treatment [32].

Rifapentine

Rifapentine is a rifamycin antibiotic with excellent antimycobacterial activity and an extended half-life compared to rifampicin [47]. It has an excellent safety profile, with infrequent hypersensitivity and hepatotoxicity as the primary adverse events. It is now a component of shortened regimens for the treatment of TB infection, (isoniazid and rifapentine for 12 weekly doses in all patients, or 30 daily doses in adults living with HIV) [48, 49]. In adults and adolescents with DS-TB, a 4-month regimen, rifapentine along with isoniazid, pyrazinamide, and moxifloxacin was non-inferior to the standard rifampicin-based 6-month regimen (Study 31, see below) [50, 51].

NEW CHILD-FRIENDLY FORMULATIONS OF TB DRUGS

There has been substantial progress in the development of child-friendly DR-TB formulations, despite the minuscule global market size of less than 2000 treatments procured annually. Fourteen quality-assured DR-TB medicines are currently available as pediatric formulations, 4 of which have multiple suppliers. Pediatric linezolid dispersible tablets are undergoing quality assurance review and when approved will mean there will be child-friendly formulations available for all WHO-recommended oral medicines in groups A, B, and C (Table 3). All formulations are quality assured by the Global Fund Expert Review Panel, the WHO Prequalification Programme, or a stringent regulatory authority [52].

Child-friendly formulations for DS-TB have been available for more than 10 years. The first fixed-dose combinations (FDCs) were launched in 2009 but soon thereafter the WHO recommended new pediatric dosing and suppliers were required to develop new FDCs. The new pediatric, dispersible FDCs to support WHO's revised dosing recommendations launched in 2015—5 years after the WHO recommendation—and include: an FDC of rifampicin 75 mg/isoniazid 50 mg and an FDC of rifampicin 75 mg/isoniazid 50 mg/pyrazinamide 150 mg.

All pediatric TB formulations are available through Stop TB's Global Drug Facility (GDF) which provides incentives and risk-sharing services for suppliers, bundled with price negotiation, pooled procurement, and technical assistance for more than 100 countries. Inequities in access exist, however, for many pediatric TB formulations. While these child-friendly TB formulations are readily available in most high-burden settings, and most low- and middle-income countries, the products are typically not available in high-income countries. Quality assurance of these products through the Global Fund Expert Review Panel and the WHO Prequalification Programme is not accepted by most high-income countries which require stringent regulatory approval [52, 53].

NEW REGIMENS FOR TB DISEASE

Drug-Susceptible Pulmonary TB

In addition to the development of child-friendly formulations and an improved understanding of pediatric-specific pharmacokinetics and safety, substantial progress has also been made in the evaluation of new regimens to treat TB disease in children.

For DS-TB, shorter treatment duration has been a central objective, and 2 recent trials have created the possibility of 4-month treatment. The Shorter Treatment for Minimal Tuberculosis in Children (SHINE) trial was a phase III randomized controlled open-label trial of 4 vs 6 months for children with symptomatic, non-severe, presumed DS, smear-negative TB disease [54, 55]. In total, 1204 children <16 years of age were randomized to (a) a 2-month intensive phase of daily isoniazid, rifampicin, and pyrazinamide (with or without ethambutol dependent on local practice) followed by a 2-month continuation phase of isoniazid and rifampicin or (b) the same intensive phase but with

Table 3. Availability of Child-Friendly Formulations of MDR/RR-TB Drugs

WHO Group	Formulation	# Suppliers	First Regulatory Approval Date	Regulator/Quality Assurance Mechanism
A	Levofloxacin 100 mg dispersible tablet	2	February 2018	WHO Prequalification
A	Moxifloxacin 100 mg dispersible tablet	2	December 2018	WHO Prequalification
A	Bedaquiline 20 mg dispersible tablet	1	May 2020	US Food and Drug Administration
A	Linezolid 150 mg dispersible tablet	2	March 2022	Global Fund Expert Review Panel
B	Clofazimine 50 mg tablet	1	January 2019	Global Fund Expert Review Panel
B	Cycloserine 125 mg mini-capsule	1	July 2018	WHO Prequalification
C	Ethambutol 100 mg dispersible tablet	2	January 2018	Global Fund Expert Review Panel
C	Delamanid 25 mg dispersible tablet	1	September 2021	European Medicines Agency
C	Pyrazinamide 150 mg dispersible tablet	2	December 2016	WHO Prequalification
C	Ethionamide 125 mg dispersible tablet	2	May 2017	WHO Prequalification

the continuation phase extended to 4 months. All drugs were dosed at the standard WHO-recommended dosages. The trial was conducted in South Africa, Uganda, Zambia, and India with the primary finding being that 4 months of treatment was non-inferior to 6 months in respect to unfavorable outcomes (failure, recurrence, death, or loss to follow-up). Based on these trial results, the WHO recommends that children <16 years of age with non-severe TB disease should be treated for 4 months. The results of another impactful treatment shortening trial were also made available in 2021. Study 31 recruited 2516 individuals aged 12 years and older with newly diagnosed pulmonary TB from 13 countries [50]. Participants were randomized to 1 of the 3 daily regimens: a standard 6-month control regimen consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol; a 4-month regimen of isoniazid, rifapentine, pyrazinamide, and ethambutol; and a 4-month regimen of isoniazid, rifapentine, pyrazinamide, and moxifloxacin. The regimen with rifapentine and moxifloxacin was non-inferior to the control regimen with similar adverse events, while the regimen with just rifapentine substituted for rifampicin did have inferior outcomes. WHO subsequently published a rapid communication suggesting that the isoniazid, rifapentine, pyrazinamide, and moxifloxacin 4-month regimen could be used to treat DS-TB in patients 12 years or older [56]. In addition, the CDC also has endorsed use of this regimen for persons aged 12 years and above [57]. To extend the use of this regimen to children, the pediatric PK and safety of rifapentine at the equivalent dose used (900 mg daily) will be evaluated in a study in development called RADIANT Kids [23].

Tuberculous Meningitis

The treatment landscape for TBM is also changing. As part of the 2022 guideline review process, WHO commissioned a systematic review and meta-analysis to compare the performance of the WHO-recommended 12-month treatment regimen (2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 10 months of isoniazid and rifampicin) with a shorter intensive regimen (6 months of isoniazid, rifampicin, and pyrazinamide all given at higher than currently recommended doses, combined with ethionamide) [25]. Mortality was lower in the 3 studies that described children treated with the intensive 6-month regimen than in the 3 studies describing children treated with the standard 12-month regimen. Following this review, WHO guidance for TBM treatment has been revised to allow the use of the intensive 6-month regimen as an alternative to the established 12-month regimen. Despite this development, it is widely acknowledged that the evidence base for TBM treatment regimens remains poor [58]. Two clinical trials are exploring TBM treatment in children. TBM-KIDS, a phase I/II trial of children with TBM in India and Malawi, randomized children to 1 of the 3 regimens for the first 2 months of treatment, with all arms then completing the same 10 months of a standard continuation phase (isoniazid and rifampicin, dosed at standard WHO-recommended dosages). For the first 2 months, the control arm comprised standard dose isoniazid, rifampicin, pyrazinamide, and ethambutol, with the first intervention arm increasing the dosage of rifampicin from 15 mg/kg to 30 mg/kg, and the second intervention arm increasing the rifampicin dosing as well as substituting levofloxacin for ethambutol [59, 60]. Results were published in 2022, and although underpowered, the study did suggest increased adverse events but improved outcomes with higher dosages of rifampicin [61]. The Short Intensive Treatment for Children with Tuberculous Meningitis (SURE) trial is a randomized trial of 6 months of enhanced anti-TB and 2 months of anti-inflammatory therapy for children with TBM [62]. Children in Zambia, Zimbabwe, India, and Vietnam are first randomized to either the standard WHO-recommended 12-month TBM regimen or to a regimen consisting of rifampicin (30 mg/kg), isoniazid (20 mg/kg), pyrazinamide (40 mg/kg), and levofloxacin (20 mg/kg) daily for 6 months. Children are then randomized to receive 8 weeks of either aspirin or placebo at the start of therapy. The study started recruitment in 2021 and is due to complete in 2023. While both TBM-KIDS and SURE use a dosage of rifampicin of 30 mg/kg, modeling studies suggest that much higher dosages may be needed [63]. As previously noted, the Opti-Rif trial explored short-term dosages of up to 75 mg/kg [46], finding higher dosages to be generally well tolerated with few adverse events.

Multidrug-Resistant/Rifampicin-Resistant TB

Developments in MDR/RR-TB treatment regimens over the last 5 years have also been exciting. Before 2015, injectable agents—often given intramuscularly in high TB-burden countries—were a cornerstone of regimen construction for adults and children [5, 64]. Although outcomes for children treated for MDR/RR-TB were generally good, therapy was very long (18 months being standard) and the injectable drugs caused pain, and hearing loss in 25%-50% of children treated [8]. Following first observational data [38] and then the STREAM clinical trial [65], a shortened 9- to 12-month standardized regimen, including an injectable drug for the first 4 months, became increasingly recognized as an effective regimen. In the 2016 update to the WHO treatment guidelines for DR-TB, children were eligible for this shortened 9- to 12-month standardized regimen. In addition, for children treated with a longer tailored regimen, this guideline suggested for the first time that the injectable drug could be omitted in cases of non-severe disease [66]. In 2017, the South African National TB Programme substituted the injectable drug in the shorter regimen with bedaquiline and generated substantial observational data to support an all-oral bedaquiline-containing shorter regimen [24]. In the 2020 WHO guideline, 3 regimens were recommended [24]: (1) a shorter all-oral bedaquiline-containing standardized regimen; (2) a longer tailored regimen; and, (3) BPaL. At that time, bedaquiline was only recommended for children over 6 years and delamanid only for

children over 3 years. The BPaL regimen was recommended for individuals aged 14 years and older who had MDR-TB with additional resistance to the fluoroquinolones [24]. In updated 2022 WHO guidelines, bedaquiline and delamanid were recommended for all ages, consequently allowing bedaquiline to be used in both the shorter all-oral bedaquiline-containing regimen and the longer regimen for children of all ages; in addition, delamanid could be used in the longer regimen for children of all ages [25]. While WHO continues to support a "shorter" standardized regimen or a "longer" tailored regimen, many experts feel that treating children with the best available drugs (including linezolid, bedaquiline, and fluoroquinolone) together with additional effective drugs (cycloserine, clofazimine, and delamanid) will mean that shorter treatment durations (eg, 6-9 months for non-severe disease, and 9-12 months for more severe disease) are possible [67].

FUTURE DIRECTIONS

In addition to the pipeline of new TB drugs, there is also an extensive list of ongoing or completed clinical trials to evaluate new drug combinations for the treatment of MDR/RR-TB (found at https://www.newtbdrugs.org/pipeline/trials). While all trials exclude younger children, many lessons can be learned and applied to the pediatric population, given it is widely accepted that if efficacy is proven in adults, it can be assumed in children. The NeXT [68] and EndTB (http://endtb.org/) trials as well as several others, evaluating novel and repurposed regimens, will provide increasing evidence of the optimal combination of drugs and treatment duration. Given that pretomanid is a central drug in both the BPaL and BPaLM regimens, it is disappointing that studies to evaluate pretomanid in children have been so delayed. Further work is required to evaluate pretomanid in children and to explore if delamanid (a drug from the same class as pretomanid) could be substituted into these pretomanid-based regimens without loss in efficacy.

Another area of future research is treatment stratification, which is widely employed in other medical fields, such as cancer medicine, yet has only recently been evaluated for the treatment of TB. Yet TB is a heterogeneous disease, particularly in children with highly variable bacillary burden and treatment response. Tailoring therapy to the disease phenotype and response to treatment would be likely to reduce treatment duration for many children, limiting toxicity and cost [69, 70]. The results of the SHINE trial demonstrate that children with non-severe disease can be treated for a shorter duration than those with more severe disease. Biomarker- or radiology-driven regimen construction and treatment duration, either at diagnosis or on treatment, could tailor therapy yet further.

Finally, the case-detection gap in children must be closed. In 2018, member states of the U.N. committed to treating 3.5 million children for TB in the 5 years between 2018 and 2022 with a commitment to treating 115 000 for MDR-TB [4]. Unfortunately, progress toward meeting these targets has fallen well short, a situation that may be exacerbated further by the global coronavirus disease 2019 (COVID-19) pandemic. Children cannot benefit from the many important advances in treatment if they are never identified, diagnosed with TB, and started on treatment.

CONCLUSION

The new TB drugs and regimens discussed here represent some of the most exciting and transformative updates to the treatment of DS- and DR-TB in children in decades. It is critical that these new approaches are scaled up efficiently to ensure that children in the field are able to benefit. Additional investment in pediatric TB therapeutics research is needed to reduce delays in the pediatric evaluation of new drugs and treatment approaches, ensuring access for children to the best possible treatment of all forms of TB.

Notes

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