Momentum in the Pediatric Tuberculosis Treatment Pipeline

By Lindsay McKenna

Introduction

Years of building advocacy and research capacity have finally brought about clinical research for children with tuberculosis (TB). While data gaps and delays between adult and pediatric approvals remain large, there is more activity in the pediatric TB treatment pipeline than ever before.

A recently published consensus on how to shorten the time between adult and pediatric approvals is expected to help expedite research in adolescents and children. A group of experts convened by the U.S. National Institutes of Health (NIH) recommends that pediatric investigation of new TB drugs and regimens begin as soon as efficacy and safety have been established in adults (phase IIb studies).[1] It also recommends that cohorts for pharmacokinetics (PK) and safety studies in children be recruited in parallel, as sequential enrollment does not necessarily offer additional protection for younger children.[2] Furthermore, it suggests the inclusion of adolescents ≥10 years old in TB drug trials at phase IIb and later, as there is no physiological reason for their exclusion.[3]

Investments in pediatric TB research and development (R&D) are also necessary to shrink existing data gaps between adults and children. The World Health Organization's *Roadmap for Childhood Tuberculosis* estimates that between 2011 and 2015, $200 million[4] would be needed for pediatric TB research.[5] At the midpoint of the 2011–2015 period, donors had spent just one-fourth of the targeted $200 million – a significant shortfall in funding for pediatric TB R&D. In 2013, TAG's annual *Report on Tuberculosis Research Funding Trends* uncovered just $25.3 million spent on pediatric TB R&D from 19 donors worldwide.[6] Of the $25.3 million invested in pediatric TB research, the largest share went to drug development: $10.8 million (43% of the total).[7] One-fifth of the total $25.3 million, or $4.7 million, was invested by the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) at the NIH.[8] UNITAID's $3.4 million investment in the STEP-TB project was enough to make it the third largest funder of pediatric TB R&D.[9] The reach of these and other investments is documented here.

Disease Burden Estimates

TB Type	Estimated Numbers of Affected Children
Drug-sensitive TB infection	**7.6 million**
Drug-sensitive TB disease	**500,000–1 million**
Drug-sensitive TB disease and HIV	**32,500**
Multidrug-resistant TB infection	**400,000**
Multidrug-resistant TB disease	**50,000**

Sources:

Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014 May 3;383(9928):1572–9. doi: 10.1016/S0140-6736(14)60195-1.

Dodd PJ, Gardiner E, Coghlan E, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Global Health. 2014 July 9;2(8):e453–9. doi: 10.1016/ S2214-109X(14)70245-1.

World Health Organization. Global tuberculosis report 2014. Geneva: World Health Organization; 2014. Available from: http://www.who.int/tb/publications/global_report/en/.

Beccerra MC, Swaminathan S. A targets framework: dismantling the invisibility trap for children with drug-resistant tuberculosis. Journal of Public Health Policy. 2014 Sept 11;35(4):425–54. doi:10.1057/jphp.2014.35.

Pediatric Pipeline Overview

Researchers continue to play catch-up on pediatric PK data for second-line TB drugs to inform World Health Organization (WHO) dosing recommendations required to advance development of pediatric formulations. Pediatric PK and safety studies of new TB drugs are progressing, albeit at varying rates. Studies under way or starting soon will evaluate preventive therapy for children exposed to multidrug-resistant TB (MDR-TB) and whether it is possible to shorten treatment for less severe forms of TB from six to four months (SHINE) and for tuberculous meningitis (TBM) (SURE-TBM) from 12 to 6 months in children. And appropriately dosed pediatric formulations of first-line TB drugs are approaching market introduction. Table 1 provides an overview of ongoing and planned TB prevention and treatment studies in children.

Table 1. Ongoing and Planned TB Prevention and Treatment Studies in Children

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Enrollment complete; results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–17 years old with LTBI	CIHR, McGill University
TBTC 35 PK and safety of rifapentine/isoniazid FDC for prevention of TB	Planned; opening Q1 2016; results expected 2018	HIV-negative infants, children, and adolescents 0–12 years old with LTBI; children ≤6 years old will get pediatric formulation	TBTC, Sanofi
TB-CHAMP 6 months levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2016; results expected 2019	HIV-positive or HIV-negative infant and child household contacts 0–5 years old; children ≤5 years old will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/ IMPAACT 2003 (PHOENIX) 6 months levofloxacin vs. isoniazid for prevention of MDR-TB	Planned; opening 2016; results expected 2020	HIV-positive or HIV-negative infant, child, and adolescent (and adult) household contacts	NIAID
V-QUIN 6 months levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2015; results expected 2020	HIV-positive or HIV-negative infant, child, and adolescent (and adult) household contacts	NHMRC
TREATMENT – NEW DRUGS			
232 PK and safety of delamanid; OBR for treatment of MDR-TB NCT01856634*	Enrolling; results expected 2017	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
233 6 months of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; results expected 2017	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT CS 5004 PK and safety of delamanid for treatment of MDR-TB	Planned; opening Q1 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	IMPAACT
JANSSEN C211 PK and safety of bedaquiline; OBR for treatment of MDR-TB NCT02354014*	Planned; opening Q2 2015	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen

Study/Regimen	Status	Population(s)	Sponsor(s)
IMPAACT P1108 PK and safety of bedaquiline; OBR for treatment of MDR-TB	Planned; opening 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, IMPAACT
TB Alliance TBD PK and safety of pretomanid for treatment of TB	Planned; opening 2018	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB; cohorts to be enrolled simultaneously/in parallel	TB Alliance
TREATMENT – EXISTING DRUGS			
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrollment complete; results expected June 2015	HIV-positive or HIV-negative infants <12 months old with TB	UNITAID/TB Alliance (Step-TB Project)
PK-PTBHIV01 PK of FLDs using 2010 WHO dosing guidelines for treatment of TB NCT01687504*	Enrolling; results expected 2017	HIV-positive or HIV-negative children 3 months to 14 years old with TB	NICHD
SHINE 4 vs. 6 months using 2010 WHO dosing guideline–adjusted FLD FDCs for treatment of minimal TB	Planned; opening 2015	HIV-positive or HIV-negative infants, children, and adolescents 0–16 years old with minimal TB	BMRC, DFID, Wellcome Trust, UCL
TBM-KIDS Safety and efficacy of high-dose rifampin +/- levofloxacin for treatment of TBM	Planned; opening Q3 2015	HIV-positive or HIV-negative infants and children with TBM	NICHD
SURE-TBM Safety and efficacy of high-dose rifampin and isoniazid, levofloxacin, and pyrazinamide to shorten treatment of TBM	Planned; awaiting funding decision	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with TBM	BMRC, Wellcome Trust, DFID (pending)
MDR-PK 1 PK and safety of SLDs for treatment of MDR-TB	Enrolling; results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
MDR-PK 2 PK, safety, and dose optimization of SLDs for treatment of MDR-TB	Planned; opening 2015	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB	NICHD, SA MRC
COTREATMENT WITH ARVS			
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB	NICHD, UNITAID/ TB Alliance (Step-TB Project)
IMPAACT P1106 PK of rifampin and isoniazid with nevirapine or lopinavir/ritonavir NCT02383849*	Enrolling; opening 2015	HIV-positive or HIV-negative low-birth-weight/ premature infants	NIAID, NICHD, IMPAACT
Rifabutin-PK PK and safety of rifabutin for treatment of TB	Planned	HIV-positive children and adults on PI-based ART with second-line ARVs	ICMR, NACO

Study/Regimen	Status	Population(s)	Sponsor(s)
IMPAACT P1070 PK and safety of efavirenz with rifampin-containing TB treatment NCT00802802*	Enrolling; results expected 2016	HIV-positive children 3 months to <3 years old with TB	NIAID, IMPAACT
PK and safety of efavirenz with rifampin-containing TB treatment NCT01704144*	Enrolling; results expected 2017	HIV-positive children and adolescents 3–14 years old with TB	NICHD
PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment NCT02348177*	Enrolling; results expected 2016	HIV-positive infants and children with TB weighing 3–15 kg	DNDi
PK and safety of nevirapine with rifampin-containing TB treatment NCT01699633*	Enrolling; results expected 2017	HIV-positive children 3 months to 3 years old with TB	NICHD
IMPAACT P1101 PK and safety of raltegravir with rifampin-containing TB treatment NCT01751568*	Enrolling; results expected 2016	ARV-naive, HIV-positive children and adolescents 2–12 years old with TB	NIAID, IMPAACT, PENTA
EARNEST PK and safety of rifabutin with lopinavir/ritonavir NCT01663168*	Discontinued; insufficient sample size	HIV-positive adults and adolescents ≥12 years old	BMRC, Abbott

*National Institutes of Health clinical trial identifiers; for more information go to ClinicalTrials.gov.

ART: antiretroviral therapy
ARV: antiretroviral
BMRC: British Medical Research Council
CIHR: Canadian Institutes of Health Research
DFID: Department for International Development (United Kingdom)
DNDi: Drugs for Neglected Diseases
FDC: fixed-dose combination
FLD: first-line drug
ICMR: Indian Council of Medical Research
IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health
LTBI: latent tuberculosis infection
NACO: National AIDS Control Organization (India)
NHMRC: National Health and Medical Research Council (Australia)
NIAID: National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health
NICHD: National Institute of Child Health and Human Development, U.S. National Institutes of Health
OBR: optimized background regimen
PENTA: Pediatric European Network for Treatment of AIDS
PI: protease inhibitor
PK: pharmacokinetics
SA MRC: South African Medical Research Council
SLD: second-line drug
TB: tuberculosis
TBD: to be determined
TBM: tuberculous meningitis
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
UCL: University College London
WHO: World Health Organization

Pharmacokinetics and Safety Data Updates

Preliminary analyses of data from an ongoing PK and safety study of second-line TB drugs determined that children are being underdosed for several drugs at the currently recommended mg/kg doses.[10,11,12,13,14] New data are emerging from PK and safety studies of first- and second-line drugs in children.

First-Line Drugs

In 2010, the WHO recommended higher doses of first-line TB drugs for children.[15] DATiC evaluated PK targets with these doses in HIV-positive and HIV-negative children and found that 12 mg/kg of isoniazid (recommended range: 7–15 mg/kg) and 35 mg/kg of pyrazinamide (recommended range: 30–40 mg/kg) achieved drug exposures in children comparable to those in adults.[16] But exposures following 15 mg/kg of rifampin (recommended range: 10–20 mg/kg) were variable, with only 17 percent (N = 47) of children achieving adult exposures and reduced exposures in the lowest and highest weight categories.[17]

A study of isoniazid in low-birth-weight and premature infants achieved comparable drug exposure to that observed in adults treated with 10 mg/kg of isoniazid.[18] There was reduced elimination in smaller and younger infants and in slow acetylators – those with a genetically determined trait marking slower metabolism of drugs processed in the liver – which suggests that exceeding the 10 mg/kg dose should be done with caution.[19] Dosing recommendations in infants less than 12 months of age are expected in the second quarter of 2015.[20]

Second-Line Drugs

Preliminary analysis of data from MDR-PK, a PK and safety study of second-line drugs in HIV-positive and HIV-negative children, found that moxifloxacin was well tolerated by children 7–15 years old.[21] With doses of 10 mg/kg (recommended range: 7.5–10 mg/kg), children achieved lower drug exposures than adults.[22] HIV-positive children taking antiretrovirals (ARVs) achieved lower moxifloxacin exposures than HIV-negative children. [23] But the sample size was too small to make accurate predictions about the effects of ARVs on drug exposure.[24]

When levofloxacin was given at 15 mg/kg (recommended range: 7.5–10 mg/kg) in the MDR-PK study, children achieved lower drug exposures than adults.[25] A recent population PK analysis of children treated for MDR-TB disease or infection in the Federated States of Micronesia and Republic of Marshall Islands found that children given 10–20 mg/kg of levofloxacin achieved the minimum inhibitory concentration (minimum drug concentration necessary to inhibit TB bacterial growth).[26]

These data suggest the need for revised doses for second-line drugs in children. More data for both moxifloxacin and levofloxacin in children are expected in the next year.

New Drugs

Otsuka, the sponsor of delamanid, has completed enrollment of the first (12–17 years old; 100 mg twice daily) and second (6–11 years old; 50 mg twice daily) age cohorts in its PK and safety study in HIV-negative children (232/233).[27] Preliminary analysis found slightly higher drug exposures among 12- to 17-year-olds compared with adults, but no safety signals.[28]

Pharmacokinetics and Safety Data Gaps

Significant PK and safety data gaps in children remain, and further research is necessary to determine optimal drug doses and regimens and to ensure safe and effective levels of drug exposure in children. Ongoing and planned studies will help address these gaps; however, many of these data should have been collected years ago, reflecting the historic neglect of children in TB research.

First-Line Drugs

Most PK and safety data gaps for first-line TB drugs are in young or HIV-positive children receiving antiretroviral therapy (ART). Studies (see table 1) to optimize doses of first-line TB drugs in these populations, and to evaluate the PK and safety of efavirenz, nevirapine, superboosted lopinavir/ritonavir, and raltegravir in young children on rifampin-based TB treatment, are being conducted.

Tuberculosis Trials Consortium (TBTC) Study 35, a PK, safety, and registration study of three months of once-weekly rifapentine and isoniazid (3HP) to prevent TB in children, is expected to open in early 2016 and currently plans to include only HIV-negative children. While the safety of rifapentine has been previously demonstrated in coinfected adults treated with ART-based efavirenz or nevirapine (non-nucleoside reverse transcriptase inhibitors),[29,30] and in healthy adults given raltegravir (integrase inhibitor),[31] the recommended first-line ART regimen for children younger than three years old is based on boosted lopinavir/ritonavir (protease inhibitor). Interactions between rifapentine and protease inhibitors have been observed.[32] Inclusion of HIV-positive children at least three years old and receiving non-protease inhibitor–based ART is under discussion.[33] Planned enrollment so far is limited to South African sites. If HIV-positive children are not included in TBTC Study 35, a future study of 3HP in HIV-positive children is expected.[34]

Second-Line Drugs

PK investigations of second-line TB drugs at currently recommended doses in children are nearing completion; more results from MDR-PK are expected in 2016, including for terizidone, levofloxacin, amikacin, and ethionamide, although drug-specific findings have been published and presented throughout the MDR-PK study's duration. These data analyses, along with an individual patient meta-analysis, are already under way and are being coordinated by the Desmond Tutu TB Center and Stellenbosch University, and they will inform WHO treatment recommendations, which are critical to advancing development of pediatric formulations of second-line drugs.

PK and safety data for moxifloxacin in children under seven years old remain elusive, largely a result of limitations of the existing formulation. Furthermore, the optimal dose of moxifloxacin has yet to be determined in adults (400 mg vs. 600 mg) – current pediatric PK and safety work evaluates drug exposures achieved in adults at 400 mg. Pending the study site's ability to enroll greater numbers of coinfected children, the MDR-PKstudy will aim to fill existing PK and safety gaps for second-line drugs in children who are HIV-positive and taking ARVs.

A recently awarded joint NIH/South African Medical Research Council grant will support work to further optimize the use of key second-line drugs in children.[35] Data from MDR-PKwill be used to simulate the doses required in children to approximate those achieved in adults.[36] The simulated, weight-based doses will then be prospectively assessed for PK, safety, and treatment response in HIV-negative and HIV-positive children 0–17 years old.[37] The study investigators have prioritized levofloxacin, moxifloxacin, and linezolid, but they hope to expand this work to other second-line drugs and to evaluate new pediatric formulations of second-line drugs should they become available during the study.[38]

New Drugs

The timelines for pediatric investigation of new drugs delamanid and bedaquiline remain discordant. The discordance is likely attributable to differing regulatory requirements between the European Medicines Agency (EMA), which requires studies in children, and the U.S. Food and Drug Administration (FDA), which exempts orphan drugs from pediatric studies altogether (see box 1, Regulatory Spotlight).

Otsuka, the sponsor of delamanid (approved by the EMA in April 2014), has completed enrollment of children down to six years old in its PK and safety study. Recently completed bioequivalence studies of a dispersible formulation will allow for the study of delamanid in younger children. Otsuka plans to open enrollment for the 3- to 5-year-old and 0- to 2-year-old cohorts in 2015 and has reached agreement with the EMA for parallel enrollment for these two age groups.[39]

Janssen, the sponsor of bedaquiline (approved by the FDA in December 2012), has yet to open its pediatric PK and safety study but expects to begin enrolling the first cohort in the second quarter of 2015.[40] Public funding in the form of $1.5 million from UNITAID's STEP-TB project is being used to support the development of Janssen's pediatric formulation of bedaquiline and its PK and safety study in HIV-negative children.[41]

Developer accountability for studies in HIV-positive children, which is not explicitly required under pediatric investigation plans (PIPs) approved by the EMA,[42,43] is nearly nonexistent. Janssen has shirked its responsibility to collect PK and safety data in HIV-positive children, leaving publically funded research consortia to pick up the slack. The NIH's International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group (IMPAACT) is planning to open a PK and safety study of bedaquiline in HIV-positive children in 2016 (P1108). While Otsuka is planning to collaborate with IMPAACT to collect PK and safety data for delamanid in HIV-positive children, U.S. taxpayers will ultimately also foot the bill for this work (IMPAACT CS 5004).

The TB Alliance has started enrolling its phase III study of pretomanid (PA-824), moxifloxacin, and pyrazinamide (together known as PaMZ) in adults, and although it has a pediatric plan in place, further preclinical toxicology work and a semen substudy are required before PK and safety studies of pretomanid can advance in children.[44] Once these data are available, the TB Alliance plans to enroll all age cohorts simultaneously or "in parallel" in accordance with recommendations issued in a consensus statement by an NIH-convened group of experts.[45]

Further complicating the investigation of pretomanid in children is an outstanding question of whether 100 mg or 200 mg is the optimal dose in adults.[46] Analysis of data collected in the phase III trial will answer this question, but not before late 2017 or early 2018.[47] This information is required to determine target drug exposures in children and to evaluate the safety of pretomanid at the correct dose. In the meantime, data on the appropriate dose of moxifloxacin (the "M" in PaMZ) in young children are urgently required.

Sutezolid is another drug for which limitations of adult data inhibit investigation in children. Sequella licensed sutezolid from Pfizer in 2012, and development has stalled since then. Early-stage phase I and II studies of sutezolid conducted by Pfizer before the transition were insufficient to determine the optimal dose in adults[48] – information required for setting the target exposures necessary to advance PK and safety studies in children. Unfortunately, Sequella has done little to advance the development of sutezolid, leaving it suspended in phase II and inaccessible to interested outside investigators.

Box 1. Regulatory Spotlight: FDA versus EMA

Regulatory authorities' ability and responsibility to hold pharmaceutical companies accountable for pediatric investigations is key to closing the gap between adult and pediatric access to new TB drugs and regimens.

The EMA requires submission of a PIP with new drug applications, whereas the Orphan Drug Act[49] allows the FDA to exempt drugs for indications granted an orphan designation (such as TB) from pediatric studies normally required under the Pediatric Research Equity Act.[50] The FDA's subpar alternative to a PIP requirement attempts to encourage research in pediatric populations by offering an additional six months of marketing exclusivity under the Best Pharmaceuticals for Children Act (BPCA).[51] Such opt-in alternatives have proved less effective at ensuring timely completion of pediatric investigations compared with the standard regulatory requirements, especially for orphan drug markets, which are perceived to be small and in which competition is sparse, understandably limiting their attractiveness for just a few months of additional marketing exclusivity.

The EMA works with drug developers to establish their plans for investigation of new drugs in children. Once the EMA approves the PIP, the drug developer is expected to complete the agreed-upon studies before a prespecified deadline (see table 2). Modifications to approved PIPs are possible. While better than the FDA at requiring the inclusion of children in research plans for new TB drugs, the EMA still fails to hold companies accountable for important pediatric studies; neither the PIP for delamanid nor the PIP for bedaquiline requires investigation in HIV-positive children.[52,53] As a result, Janssen and Otsuka have eluded their responsibilities to collect PK and safety data in HIV-positive children. IMPAACT, a publically funded research consortium, is planning studies (P1108; CS 5004) to ensure that this pediatric subpopulation is not neglected and can benefit from new TB treatments.

Timely investigation of new TB drugs in HIV-positive and HIV-negative children, facilitated by the establishment of comprehensive and thoughtful regulatory policies, is critical to closing existing adult-pediatric approval and access gaps.

Table 2. Pediatric Investigation Timelines: Delamanid versus Bedaquiline

	Delamanid		Bedaquiline	
	FDA	EMA	FDA	EMA
Registration status	Not yet registered	Approved for MDR-TB in adults (≥18 years old), April 2014	Approved for MDR-TB in adults (≥18 years old), December 2012	Approved for MDR-TB in adults (≥18 years old), March 2014
PIP-required studies	1. Develop age-appropriate formulation (dispersible tablet) 2. Juvenile rat toxicity studies 3. Bioequivalence of pediatric formulation in healthy adults 4. Pharmacokinetics and safety in children 0–18 years old 5. 6-month extension study of long-term safety and efficacy		1. Develop age-appropriate formulation (dispersible tablet; granules) 2. Juvenile rat toxicity studies 3. Bioavailability of pediatric formulation in healthy adults 4. Pharmacokinetics and safety in children 0–18 years old	
Current status	Enrollment complete (children 6–18 years old) Enrollment planned 2015–16 (children ≤5 years old)		Study protocol complete; country applications submitted Opening Q2 2015	
PIP execution deadline	April 2017		September 2020	

Pediatric Formulations

Treatment of children with TB often necessitates the cutting and crushing of tablets. Five years after the WHO released revised pediatric dosing guidelines for first-line drugs, the market introduction of appropriately dosed pediatric formulations is finally in sight. This is in stark contrast to the situation for second-line drugs, for which we are still determining the pediatric mg/kg dose ranges that will achieve drug exposures comparable to those in adults. While the market introduction of pediatric formulations of second-line drugs may seem far away, there is some reason for optimism. Recent progress in formulation development expected to improve existing medicines for children, their caregivers, and the health care systems supporting their care is summarized in table 3.

Table 3. Pediatric Evidence and Formulation Summary by TB Drug

Drug	Studied in Children	Evidence-Based Dosing Guidance Available	Appropriate Pediatric Formulation Exists/Is in Development	Formulations in the Pipeline
FIRST-LINE DRUGS				
Isoniazid	✓	✓ (WHO)	✓	Updated doses as dispersible tablets: HRZ: 50/75/150 mg HR: 50/75 mg H: 100 mg
Rifampin	✓	✓ (WHO)	✓	
Pyrazinamide	✓	✓ (WHO)	✓	
Ethambutol	✓	✓ (WHO)	✓	Updated dose (100 mg) as dispersible tablet
Rifapentine	✓ (≥2 yrs.)	✓ (CDC)	✓	New as dispersible tablets: HP: 150/150 mg P: 100 mg
SECOND-LINE DRUGS				
Moxifloxacin	✓ (≥7 yrs.)		✓	Updated dose (100 mg) as scored dispersible tablet
Ofloxacin	✓			
Levofloxacin	✓		✓	Updated dose (100 mg) as scored dispersible tablet
Linezolid			✓	Updated dose (150 mg) as scored dispersible tablet
Clofazimine	✓ (for leprosy)			
Terizidone	✓			
Cycloserine			✓	Updated dose (125 mg) as mini capsule
Ethionamide	✓		✓	Updated dose (125 mg) as scored dispersible tablet
Amikacin	✓		(injectable)	
PAS	✓		✓	
Delamanid	✓ (>5 yrs.)		✓	New (20 mg and 5 mg) as dispersible tablets
Bedaquiline			✓	New (20 mg) as dispersible tablet
Pretomanid				Feasibility work under way
Sutezolid				

First-Line Drugs

There are multiple pediatric formulations of first-line drugs at various stages of development.

Sanofi, the sponsor of rifapentine (indicated for use in drug-sensitive TB [DS-TB] and latent TB infection in children as young as two years old), is planning to initiate a bioavailability and safety study of a mango-flavored, fixed-dose, dispersible combination of 150 mg rifapentine with 150 mg isoniazid, as well as a separate 100 mg rifapentine dispersible to facilitate dose adjustments in young children, in the third or fourth quarter of 2015.[54,55] These formulations will then be used in TBTC 35.

The TB Alliance and the WHO Essential Medicines and Health Products department, partners on the UNITAID-funded STEP-TB project, anticipate fixed-dose combinations of HRZ (50 mg isoniazid + 75 mg rifampin + 150 mg pyrazinamide) and HR (50 mg isoniazid + 75 mg rifampin) to become available through the Global Drug Facility (GDF) by the third quarter of 2015.[56] They expect separate formulations of 100 mg ethambutol, a recommended addition to HRZ in children with extensive disease living in settings where the prevalence of HIV or of isoniazid resistance is high,[57] and 100 mg isoniazid, recommended for preventive therapy, to follow six months later.[58] All first-line products are projected to be prequalified by the WHO and on the market by the second quarter of 2016.[59]

The TB Alliance and the WHO continue to prepare countries for uptake of these long-awaited formulations. Multiple strategies are necessary. WHO prequalification, a mechanism put in place to ensure and monitor the quality of medications procured in bulk, is required of manufacturers looking to sell medications through the GDF. For countries that don't purchase pediatric medications through the GDF, namely Brazil, China, India, Indonesia, the Russian Federation, and South Africa, submission of separate in-country dossiers is required.[60] Ideally, the STEP-TB project's work will pave the way for the development and timely introduction of pediatric formulations of second-line drugs.

Second-Line Drugs

Currently, just five of 14 second-line drugs are available in pediatric preparations, and even these are inadequate.[61] Existing oral suspensions (syrups) of linezolid and levofloxacin are difficult to dose accurately, are bulky and difficult to ship and store, and are not widely available. Lucane Pharma developed a dosing spoon to ease weight-based dispensing of para-aminosalicylic acid (PAS) granules to children,[62] but providers continue to report difficulties preparing PAS, possibly from lack of awareness about the availability of this tool designed to help measure out appropriate doses.[63]

Standard formulations affect which second-line drugs are studied in and used to treat children. For example, moxifloxacin is available only in 400 mg tablets that are not scored and are bitter when crushed. As a result, it is not feasible to treat children weighing less than 20 kg (typically children younger than eight years old) within the recommended 7.5 mg/kg to 10 mg/kg range. Instead, children weighing less than 20 kg are treated with ofloxacin or levofloxacin, which are available in 200 mg and 250 mg scored tablets, respectively. Another drug that is difficult to administer to children is clofazimine, which is available only in a softgel capsule form that prohibits splitting or cutting to obtain smaller doses.

However, there is cause for tempered optimism. Macleods Pharmaceuticals has developed scored, dispersible prototypes of levofloxacin (100 mg), moxifloxacin (100 mg), linezolid (150 mg), and ethionamide (125 mg) and a minicapsule of cycloserine (125 mg).[64] TB-CHAMP, a trial to evaluate levofloxacin as preventive therapy for household MDR-TB contacts under five years old, will pilot Macleods Pharmaceuticals' 100 mg scored and dispersible levofloxacin formulation. Investigator-initiated grant funding will support further development of the levofloxacin formulation and its procurement for the trial.

Collaboration with Macleods Pharmaceuticals and shared investment are urgently needed to expedite the advancement of the remaining formulations from prototype to market, work estimated to cost $3.5 million.[65] In addition, finalized, evidence-based, and WHO-recommended mg/kg dose ranges are necessary for attracting a second manufacturer. The previously described research to determine optimal mg/kg dose ranges of second-line TB drugs in children and data from an individual patient meta-analysis should inform a pediatric treatment chapter in the WHO consolidated treatment guidelines up for review in November 2015.

Because the potential market for pediatric formulations of second-line drugs is small, it is important to encourage additional manufacturers to join the space, which will help improve the likelihood of competitive drug pricing and stable supply. To this end, it is critical that the UNITAID-funded STEP-TB project be expanded to include second-line drugs.

New Drugs

A bioequivalence study of delamanid as 5 mg and 25 mg dispersible tablets in strawberry and cherry flavors is complete.[66] The availability of these formulations will allow the continued study of delamanid in children under five years old (232; 233.

A bioavailability study of bedaquiline as a 20 mg dispersible tablet has been completed.[67] This pediatric formulation will be used in cohorts inclusive of children under 12 years old in Janssen's PK and safety study, expected to open the second quarter of 2015.[68]

The TB Alliance has begun pediatric formulation feasibility work toward a single-drug dispersible tablet of pretomanid, with eventual plans for a dispersible fixed-dose combination tablet containing pretomanid, moxifloxacin, and pyrazinamide.[69] Advance preparation of the pediatric formulation will facilitate planned simultaneous enrollment of all age groups. However, data on optimized dosing of pretomanid and moxifloxacin, especially for young children, are necessary to inform development of the planned pediatric and fixed-dose combination formulations.

Regimens

Several studies of levofloxacin to prevent MDR-TB in children are expected to begin enrolling in 2016 (A5300/P2003; TB-CHAMP; V-QUIN. Levofloxacin is also being evaluated as a component of therapy for children with TBM (TBM-KIDS; SURE-TBM). Levels of cerebrospinal fluid penetration of new drugs and their potential efficacy for the treatment of TBM remain to be explored.

A study to evaluate whether treatment can be shortened from six to four months in children with minimal DS-TB is expected to open this year (SHINE). Similar studies to evaluate whether treatment for children with drug-resistant TB can be shortened and given without an injectable agent are needed,[70] especially considering the low number of TB bacteria (paucibacillary TB disease) and high rates of hearing loss observed in children related to use of injectable drugs.[71]

Studies to evaluate improved regimens for DS-TB and MDR-TB (see "Tuberculosis Treatment Pipeline," in *2015 Pipeline Report* [publishing July 2015]) rarely include pediatric components, but some at least allow for the inclusion of adolescents (≥10 years old). Table 4 provides an overview of ongoing and planned adult studies that include adolescents, a population for which we have a first-ever global estimate of TB disease burden: 655,000 cases per year.[72] Adolescent inclusion in phase III adult trials is especially warranted as there is no physiological basis for exclusion – adolescents achieve similar levels of drug exposures as adults, present with similar forms of TB disease, and tolerate adult formulations.

Table 4. Ongoing and Planned Adult TB Studies That Include Adolescents

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
ACTG A5279 4 weeks of daily rifapentine and isoniazid for prevention of TB NCT01404312*	Enrolling; results expected 2018	HIV-positive adults and adolescents ≥13 years old with LTBI	NIAID, ACTG, IMPAACT
ACTG A5300/ IMPAACT 2003 (PHOENIX) 6 months levofloxacin vs. isoniazid for prevention of MDR-TB	Planned; opening 2016; results expected 2020	HIV-positive or HIV-negative infant, child, adolescent, and adult household contacts	NIAID
V-QUIN 6 months levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2015; results expected 2020	HIV-positive or HIV-negative infant, child, adolescent, and adult household contacts	NHMRC
TREATMENT			
TBTC 31 Safety and efficacy of rifapentine-containing regimens to shorten treatment of TB	Planned; opening 2015	HIV-negative and HIV-positive adults and adolescents ≥12 years old with TB	TBTC
TRUNCATE-TB Safety and efficacy of 2-month new regimens for treatment of TB	Planned; opening 2015	HIV-negative and HIV-positive, treatment-naive adults with TB; planned inclusion of adolescents ≥12 years old delayed pending Janssen C211	UCL, BMRC, Wellcome Trust, DFID, NMRC
NiX-TB Safety and efficacy of PaLJ(Z) to shorten treatment of XDR-TB NCT02333799*	Enrolling; results expected 2021	HIV-negative and HIV-positive adults and adolescents ≥14 years old with XDR-TB	TB Alliance
ReDEFINe Safety and efficacy of high-dose rifampin for treatment of TBM NCT02169882*	Enrolling; results expected June 2016	Adults and adolescents ≥15 years old with TBM	USAID
endTB Safety and efficacy of new bedaquiline- or delamanid-containing regimens for treatment of MDR-TB	Planned; opening December 2015	Adults and adolescents ≥15 years old with MDR-TB	UNITAID, MSF, PIH, IRD
*National Institutes of Health clinical trial identifiers; for more information go to ClinicalTrials.gov.			

ACTG: AIDS Clinical Trials Group, National Institute of Allergy and Infectious Diseases (United States)
BMRC: British Medical Research Council
DFID: Department for International Development (United Kingdom)
IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health
IRD: Interactive Research and Development
J: bedaquiline
L: linezolid
MSF: Médecins Sans Frontières
NIAID: National Institute of Allergy and Infectious Diseases (United States)
NHMRC: National Health and Medical Research Council (Australia)
NMRC: National Medical Research Council (Singapore)
Pa: pretomanid (PA-824)
PIH: Partners In Health
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
UCL: University College London
USAID: United States Agency for International Development
XDR-TB: extensively drug-resistant tuberculosis
Z: pyrazinamide

Recommendations

Stand-alone strategies focused on addressing TB in adults are insufficient to achieving the ambitious targets set forth in the End TB Strategy.[73] Recent recognition within the field of the importance of expanding prevention and treatment of pediatric TB has resulted in an increasingly full roster of studies in children. Yet much work remains to be done to expedite studies of regimens and new drugs in children and to advance the development of pediatric formulations of second-line drugs.

Expedite investigation of new drugs and regimens in children.

For drug companies

Pediatric investigation of new TB drugs and regimens should begin as soon as efficacy and safety have been established in adults (phase IIb studies); cohorts for PK and safety studies in children should be recruited in parallel; and adolescents ≥10 years old should be included in TB drug trials phase IIb and later.[74] These recommendations require drug sponsors and investigators planning studies of new TB drugs and regimens in adults to consider work necessary for facilitating eventual expansion of the targeted indication to children early on. Upstream decisions and lack of planning greatly (and often adversely) affect pediatric research and access timelines. Ultimately, knowledge gained from investigations focused on individual drugs should inform the design and implementation of pediatric-friendly treatment regimens (e.g., a nine-month, injection-sparing regimen for MDR-TB in children that incorporates optimized doses of existing and new TB drugs).

For regulatory authorities

More thoughtful requirements from stringent regulatory authorities will also help ensure the timely inclusion of children in TB research. The Orphan Drug Act should be amended so that it does not allow drugs exemption from the Pediatric Research Equity Act when additional pediatric-specific data are necessary for an indication in children younger than 18 years old. The Pediatric Research Equity Act should explicitly require investigation in all affected pediatric subpopulations. Similarly, the EMA Pediatric Committee on PIPs should work with drug sponsors to ensure the inclusion of HIV-positive children in planned investigations of new TB drugs.

Advance the development of pediatric formulations of second-line drugs.

- The WHO must issue formal dosing recommendations for second-line TB drugs in children and invite expressions of interest for pediatric formulations in line with its dosing recommendations. These two steps are required before the development of urgently needed pediatric formulations can advance.
- In tandem, the UNITAID-funded STEP-TB project should be expanded to take forward existing pediatric formulation prototypes of second-line TB drugs and to provide incentives for competing manufacturers to enter the market.

Increase investments in pediatric TB research and development.

- The trend of inadequate pediatric TB R&D funding must be reversed if we are to achieve zero TB deaths, new infections, suffering, and stigma, especially before 2035.
- The NICHD should continue to support studies critical to improving treatment of pediatric TB and to filling both long-standing and new gaps in pediatric PK and safety data, especially for HIV-positive children taking ARVs.
- UNITAID should expand funding for the STEP-TB project to facilitate expedited market introduction of pediatric formulations of second-line and new TB drugs, especially given the limited market size and lack of interest from manufacturers. Public money should be complemented by investment and commitment from manufacturers entering the pediatric TB market.

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