Pipeline Report » 2019

Pediatric Tuberculosis Diagnosis, Treatment, and Prevention

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Pediatric Tuberculosis Diagnosis, Treatment, and Prevention

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Introduction

Less than half of the estimated 1 million children sick from tuberculosis (TB) in 2018 were diagnosed and reported to the World Health Organization (WHO).[1] An estimated 230,000 children died of TB in 2018, among whom 80 percent were younger than five years old. Ninety-six percent of child deaths from TB occur before treatment is ever started.[2]

Large gaps in the detection, treatment, and prevention of TB among children reflect a historical lack of political will and the persistent limitations of the tools we have for addressing TB in children. The only vaccine for TB, bacillus Calmette–Guérin (BCG), confers limited protection that wanes after childhood. The gold-standard diagnostic tool, culture, misses 80 percent of children with clinically diagnosed TB. TB treatment and prevention regimens are long, assume one size fits all (despite the variety of forms in which TB disease presents in children), and often contain medicines not yet available in child-friendly forms.

Encouragingly, global leaders are increasingly aware of and committed to addressing the needs of children and families affected by TB. The political declaration from the 2018 United Nations High Level Meeting (HLM) on TB includes pediatric-specific diagnosis, treatment, and prevention targets, as well as commitments to increase funding for TB research and development (R&D), including for tools and interventions that meet the needs of children.[3]

In 2018, Treatment Action Group's annual *Report on Tuberculosis Research Funding Trends* reported a doubling of investments in pediatric TB research, taking the global total from US$29.1 million to $56 million.[4] Funding opportunity announcements and requests for proposals from the United States National Institutes of Health (NIH) and the European and Developing Countries Clinical Trials Partnership signal that the governments of the United States and European countries intend to tackle the most pressing and difficult areas of work—TB meningitis and early and rapid diagnostics.[5,6,7,8]

Donor support for introducing and scaling up new tools and interventions to improve the diagnosis, treatment, and prevention of TB in children is also apparent. Unitaid is supporting the Elizabeth Glaser Pediatric AIDS Foundation CaP TB Project (Catalyzing Pediatric Tuberculosis Innovations), which will introduce and scale up new diagnostics, formulations, and models of care for pediatric TB in nine sub-Saharan African countries and India by 2021. The Stop TB Partnership Global Drug Facility is working in close partnership with the Sentinel Project on Pediatric Drug-Resistant TB to introduce new pediatric formulations of medicines for drug-resistant TB in 17 countries. Donors should continue to support and expand these initiatives, especially as new evidence and tools emerge.

The pediatric TB research pipeline has produced incremental gains and is increasingly dynamic, responding to developments in the adult space and forging new paths designed specifically to address the unique needs of children with TB. Continued investments in pediatric dosing and safety studies will be necessary to keep up with ongoing TB treatment and prevention optimization work in adults and to inform the use of future TB treatment and prevention medicines and regimens in children. The pediatric TB diagnostics space warrants special attention given the amount of work left to do, especially related to the design, quality, and reporting of studies evaluating biomarkers of childhood TB.[9] Researchers evaluating TB diagnostics in children should stratify data by age and better focus recruitment on younger children.

The Pediatric TB Diagnostics Pipeline

Existing tests and those under development that are designed to detect TB bacteria are suboptimal for children, who often have fewer TB bacteria in their bodies than adults (paucibacillary disease). The usefulness of sputum-based tests is limited in young children, who often have difficulty producing sputum and have high rates of extrapulmonary TB. Even using the gold standard of culture, microbiological confirmation of TB is obtained in only 15–20 percent of children with clinically diagnosed TB. Several methods of TB diagnosis exist or are under investigation. These include direct detection of Mycobacterium tuberculosis (MTB), detection of MTB antigens, and detection of the host-immune response to MTB.

Testing and optimizing the performance of existing tests in children remains important, and efforts are underway, including evaluating the performance of nucleic-acid amplification tests (i.e., Xpert MTB/RIF) on sample types other than sputum and antigen-based tests in children. The new Xpert Ultra assay is expected to have improved sensitivity in all sample types. Two retrospective studies using cryopreserved sputum samples found an 11 percent higher sensitivity of Xpert MTB/RIF Ultra compared with Xpert MTB/RIF.[10] The Unitaid-funded TB-Speed Pneumonia study (NCT03831906) will assess Ultra on nasopharyngeal aspirates (NPAs) and stool samples from children under five years old with severe pneumonia, a common TB co-infection in young children (results expected 2021). The TB-Speed investigators will ultimately assess the impact on child mortality of adding systematic early detection of TB using Ultra, performed on NPAs and stool samples, to the standard of care for children with severe pneumonia. RaPaed-TB (Rapid and Accurate Diagnosis of Pediatric TB; NCT03734172) is a platform study for the evaluation of new TB diagnostics in children that opened in early 2019. Urine, blood, stool, and other specimens from children with confirmed, clinically diagnosed, or unlikely TB will be used to evaluate the sensitivity and specificity of new test candidates (including Ultra and the next-generation LAM test by Fujifilm) against microbiological and clinical reference standards.[11]

To radically improve rates of diagnosis in children with TB, a rapid diagnostic test that works on easier-to-obtain samples than sputum and/ or the host's response to TB is likely required. Considering age-dependent differences in the immune response to TB and the broad spectrum of TB disease observed in children, it is encouraging to see the TB diagnostics research community and funders increasing their efforts to scale up pediatric-specific discovery, validation, and implementation research efforts to develop novel assays that can detect TB antigens, host markers, or gene signatures (genes differentially expressed under certain biological or other conditions, for example, in the presence of TB infection or disease) in children.

The following table (Table 1) provides information on select non-sputum pathogen detection approaches, antigen-based assays, host marker-based assays, and gene signatures that are in development and undergoing evaluation for use in children. A systematic review of biomarkers under investigation between 2000 and 2017 for the diagnosis of pulmonary TB in children concluded that the performance of biomarkers included in the review showed promise, but require further refinement and optimization to meet the WHO-recommended minimal targets* for a new diagnostic or triage test for TB, and should be evaluated in multicenter prospective studies in diverse geographical locations and clinically relevant populations.[12]

Table 1. Assays and Gene Signatures Under Evaluation for the Detection of TB Infection and Disease in Children

Assay Name	Signature/Biomarker and Indication	Company/ Sponsor(s)	Location(s) of Pediatric Study Cohorts	Status
Xpert MTB/RIF on stool	MTB complex in stool For detecting TB disease in children	Cepheid/ FIND	Burkina Faso, Cambodia, Cameroon, India, Kenya, Malawi, Mozambique, Pakistan, South Africa, Tanzania, Uganda, Vietnam, Zimbabwe	WHO guidance issued in 2013; data available on the utility of Xpert on stool were limited and not considered in the analysis[13]
Pediatric studies of Xpert MTB/RIF on stool samples compared with those on sputum or gastric aspirate samples report sensitivities of 32–90 percent with specificities of 97–100 percent. Sensitivity was higher in HIV-positive children and among children who were hospitalized or with more severe disease.[14,15,16,17,18,19,20] **A systematic review and meta-analysis found the pooled sensitivity and specificity of Xpert MTB/RIF on stool was 67 percent and 99 percent, respectively, compared with culture or Xpert MTB/RIF on specimens used to diagnose TB in children (expectorated sputum, nasogastric aspirates, gastric lavage fluid, and nasopharyngeal aspirates). Compared to a clinical reference standard, the pooled sensitivity and specificity of Xpert MTB/RIF on stool was 22 percent and 100 percent, respectively. These data suggest that Xpert MTB/RIF on stool may have utility as a rule-in test.[21]** **Sample processing methods are being explored to optimize the use of Xpert MTB/RIF on stool for diagnosing TB in children.[22] A new stool-processing kit designed to be used in conjunction with Xpert MTB/RIF is being developed by the Foundation for Innovative Diagnostics and Rutgers University (the Alland Laboratory). Larger clinical studies are needed to validate different stool sample processing methods and their impact on the sensitivity and specificity of Xpert MTB/RIF and more sensitive assays, such as Ultra. A standardized stool sample preparation protocol and additional research specifically in children <5 years old are also needed.**				

* WHO minimal target for a new TB diagnostic test: 66 percent sensitivity and 98 percent specificity; a new triage test: 90 percent sensitivity and 70 percent specificity.

Assay Name	Signature/Biomarker and Indication	Company/ Sponsor(s)	Location(s) of Pediatric Study Cohorts	Status
Xpert MTB/RIF on NPAs	MTB complex in NPAs For detecting TB disease in children	Cepheid	Burkina Faso, Cambodia, Cameroon, India, Malawi, Mozambique, South Africa, Tanzania, Vietnam	WHO guidance issued in 2013; data available on the utility of Xpert MTB/RIF on NPAs were too limited[23]
A pediatric study of Xpert MTB/RIF on repeat NPAs compared with culture on NPA or induced sputum reported 65 percent sensitivity (71 percent for Xpert MTB/RIF on induced sputum) and 98.2 percent specificity (99.1 percent for Xpert MTB/RIF on induced sputum). Xpert MTB/RIF testing on a second NPA produced a 36.7 percent increase in yield, suggesting the utility of Xpert MTB/RIF on repeat NPAs in settings where, or in children for whom, induced sputum or culture is not feasible.[24] **A pediatric study of Xpert MTB/RIF on NPAs only and NPAs plus stool compared with culture in HIV-positive children reported 62.5 percent and 75.0 percent sensitivity and 100.0 percent and 99.4 percent specificity, respectively (on standard samples [sputum or gastric aspirate] Xpert MTB/RIF demonstrated 81.3 percent sensitivity and 98.2 percent specificity). These findings suggest the potential utility of combinations of alternative samples that are easier to collect for diagnosing TB in children.[25]**				
Determine TB LAM Ag urine test (AlereLAM)	TB antigen LAM For detecting TB disease in children living with HIV	Alere (Abbott)	Cameroon, India, Kenya, South Africa, Uganda	WHO guidance issued in 2015[26]
The Determine TB LAM Ag urine test (AlereLAM) has low sensitivity (50 percent compared with culture and 63 percent compared with Xpert in HIV-positive children) for diagnosing TB in children but predicts mortality among HIV-positive children with unconfirmed TB. AlereLAM may have potential value as a rule-in test to aid early TB diagnosis in HIV-positive children.[27,28] **The Fujifilm SILVAMP TB LAM urine test (FujiLAM) is expected to offer improved sensitivity (30 percent higher sensitivity than AlereLAM; 70.4 percent compared with 42.3 percent) but has yet to be evaluated for children.[29]**				
C-Tb skin test	TB antigens ESAT-6 and CFP10 For determining TB infection in children	The Statens Serum Institute	South Africa, Spain	
C-Tb, TST, and IGRAs performed equally well at determining TB infection in children, but low CD4+ T-cell counts (<100 cells/mm3) may reduce C-Tb test performance.[30,31] **C-Tb and TST test positivity rates and the median induration size were significantly reduced among symptomatic children <5 years old (in line with WHO recommendations, IGRAs were not performed in this age group) compared with asymptomatic children. The authors speculate that this may be due to the immune-suppressive effect of TB and advise that negative test results be interpreted carefully.[32]**				
TAM-TB blood test	T-cell activation and maturation markers (CD38 and CD27) For detecting TB disease in children	University Hospital, LMU (University of Munich); German Center for Infection Research (DZIF)	India, Malawi, Mozambique, Tanzania	Undergoing further development and evaluation
Compared with culture, the TAM-TB assay demonstrated 83 percent sensitivity among children with culture-confirmed TB and 96.8 percent specificity among children classified as not having TB. The sensitivity of the TAM-TB assay was 69 percent when children with highly probable TB were included alongside those with culture confirmed TB. Encouragingly, positivity rates decreased with decreasing clinical diagnostic certainty.[33]				

Assay Name	Signature/Biomarker and Indication	Company/ Sponsor(s)	Location(s) of Pediatric Study Cohorts	Status
Kaforou et al. three-gene signature	Unpublished; includes GBP5 For distinguishing TB disease from other diseases and from TB infection in children	Imperial College London	Kenya, Malawi, South Africa	Undergoing further development and evaluation
The Kaforou et al. three-gene signature (derived from the 51-gene signature identified by Anderson et al.[34]) demonstrated 93.3 percent sensitivity and 80 percent specificity in pediatric test data sets from South Africa and Malawi and 95.5 percent sensitivity and 73.1 percent specificity in a pediatric validation data set from Kenya.[35]				
Sweeney et al. three-gene signature	GBP5, DUSP3, and KLF2 For distinguishing TB infection from TB disease in children	Stanford Institute for Immunity, Transplantation and Infection	Kenya, Malawi, South Africa, Venezuela	Undergoing further development and evaluation
The Sweeney et al. three-gene signature could distinguish TB infection from culture-positive TB disease in children with 86 percent sensitivity and specificity, but TB scores (calculated by subtracting the mean expression of downregulated genes from the mean expression of upregulated genes) in children with culture-negative TB were significantly lower than those in children with culture-positive TB, suggesting lower sensitivity in children with culture-negative TB or incorrect classification of children with other diseases as having culture-negative TB.[36]				
Chegou et al. CSF signature	VEGF, IL-13, and LL-37 For detecting TBM in children	South African Medical Research Council/ Stellenbosch University	South Africa	
The Chegou et al. CSF signature distinguished TBM from other types of meningitis in children with 52 percent sensitivity and 95 percent specificity.[37] **When tested in a separate, comparable cohort, and considering values above the threshold for any one of the three markers in the signature to represent a positive result, the sensitivity of the signature improved (95.7 percent), but the specificity decreased to 37.5 percent. In the same study population, a different four-marker signature (sICAM-1, MPO, CXCL8, and IFN-γ) demonstrated a sensitivity of 87 percent and a specificity of 95.8 percent. Replacing IL-13 and LL-37 with IFN-γ and MPO increased the sensitivity of the three-marker Chegou et al. signature to 82.6 percent and specificity to 95.8 percent. Further optimization of the refined VEGF-based signature through the selection of better cut-off values resulted in improved sensitivity and specificity of 92 percent and 100 percent, respectively. Additional validation studies are necessary and should include larger numbers of children, including those living with HIV.[38]**				

CSF: cerebrospinal fluid
FIND: Foundation for Innovative Diagnostics
HIV: human immunodeficiency virus
IGRA: interferon-gamma release assay
IFN-γ: interferon-gamma
LAM: lipoarabinomannan
MTB: Mycobacterium tuberculosis
NPA: nasopharyngeal aspirates
TB: tuberculosis
TBM: tuberculous meningitis
TST: tuberculin skin test
WHO: World Health Organization

The Pediatric TB (Therapeutic) Prevention Pipeline

TB prevention research has produced WHO-recommended short-course, rifamycin-based regimens,[39] yet the inclusion of children in these studies to ensure they benefit from such advances has been inconsistent. Promisingly, studies to evaluate the use of levofloxacin (TB-CHAMP) or delamanid (PHOENIx) for the prevention of TB among close contacts of people with multidrug-resistant TB (MDR-TB) are progressing in children.

In contrast, two years have passed since a phase III trial validated a once-daily regimen of isoniazid and rifapentine (1HP) for the prevention of TB in adults and adolescents living with HIV. The pediatric research community again finds itself playing an all-too-familiar game of catch-up. A study to inform 1HP dosing for children living with HIV has become a new priority taken up by the International Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network (CS 5019). These data will have additional benefits for informing pediatric dosing for other daily rifapentine-based regimens under investigation in adults (TBTC S31 [4HPZM for drug-sensitive TB (DS-TB)]; TBTC S37 [6P for TB preventive therapy (TPT)]), though pediatric studies will still be required to define the dosing and safety of these regimens for children. An even longer established rifapentine-containing TB prevention regimen, three months of once-weekly rifapentine and isoniazid (3HP), still requires execution of a long-planned pharmacokinetics (PK) and safety study to inform dosing for children under two years old; after multiple delays, this study (TBTC 35) is expected to open before the end of 2019.

Table 2 presents an overview of TB prevention studies in children that are ongoing or planned, and Table 3 presents results from TB prevention studies in children that have been completed in recent years.

Table 2. Ongoing and Planned TB Prevention Studies in Children

Study Name	Status	Regimen	Population(s)	Funder(s)
TBTC 35 NCT03730181	Planned; opening 2019	PK and safety of 3HP \FDC for prevention of TB	HIV-positive and HIV-negative infants and children 0–12 years old with LTBI	TBTC, Sanofi
WHIP3TB NCT02980016	Enrollment complete; results expected 2020	Part A: Efficacy and safety of 3HP vs. 6H for prevention of TB Part B: Efficacy and safety of 3HP given once vs. 3HP given once a year for 2 years for prevention of TB	HIV-positive adults, adolescents, and children ≥2 years old	The Aurum Institute, USAID, KNCV
TB-CHAMP ISRCTN92TG634082	Enrolling; results expected 2022	Efficacy, safety, and PK of 6 months of daily levofloxacin vs. placebo for prevention of MDR-TB	HIV-positive and HIV-negative infant and child household contacts 0–5 years old; children will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/ IMPAACT P2003B (PHOENIx) NCT03568383	Enrolling; results expected 2025	Efficacy and safety of 6 months of daily delamanid vs. 6 months of daily isoniazid for prevention of MDR-TB	High-risk infant, child, adolescent, and adult household contacts of individuals with MDR-TB	NIAID, NICHD
V-QUIN ACTRN12616000215426	Enrolling; final results expected 2022	Efficacy and safety of 6 months of daily levofloxacin vs. placebo for prevention of MDR-TB	HIV-positive and HIV-negative adult household contacts; randomization of adolescents and children <15 years old to intervention initiated in 2019	NHMRC
IMPAACT P2024	Protocol in development	PK and safety of 1HP for prevention of TB	HIV-positive and HIV-negative children 0–15 years old	NIAID, NICHD

Table 3. Recently Completed TB Prevention Studies in Children

Study Name	Status	Regimen	Population(s)	Funder(s)
P4v9 NCT00170209	Results published 2018 (see below)	Efficacy and safety of 4R vs. 9H for prevention of TB	HIV-positive and HIV-negative infants, children, and adolescents 0–18 years old	CIHR, McGill University
Treatment with 4R was as effective as 9H for the prevention of TB in children. Both regimens were well tolerated and safe. Treatment completion rates were better for 4R.[40]				
Titi	Results presented 2018 (see below)	Implementation study of 3HR FDC or 6H for prevention of TB	HIV-positive and HIV-negative infant and child contacts <5 years old	Expertise-France/ the Union
Preliminary results were presented at the Union World Conference on Lung Health in the Hague in October 2018. The study enrolled nearly 2,000 child contacts: 5 percent (99/1,943) were diagnosed with active TB; 90 percent (1,753/1,943) were started on preventive therapy, with 92 percent completing the full course of therapy. Follow-up is ongoing.[41]				
Tshepiso [substudy]	Results published 2017 (see below)	PK and safety of nevirapine with rifampin and isoniazid for prevention of TB	HIV-exposed infants receiving nevirapine for HIV prophylaxis born to mothers with TB	NIAID
Rifampin-based TB preventive treatment significantly reduces nevirapine concentrations in HIV-exposed infants and should be avoided.[42]				
TBTC 26 (PREVENT TB) NCT00023452 NCT00164450	Results published 2015 (see below)	Efficacy, safety, and PK of 3HP vs. 9H for prevention of TB	Mostly HIV-negative child and adolescent contacts 2–17 years old	TBTC, IMPAACT
Treatment with 3HP was as effective as 9H for the prevention of TB in children. Both regimens were well tolerated and safe. Treatment completion rates were better for 3HP.[43] **A twofold greater rifapentine dose in children (23 mg/kg) resulted in drug exposures that were 1.3-fold higher compared with exposures in adults administered a standard dose (11 mg/kg) associated with successful TB prevention. Food increased bioavailability in children. Crushing tablets decreased bioavailability in children.**[44] **Weight-based dosing recommendations for rifapentine administered as 3HP to children are as follows: 10–14 kg, 300 mg; 14.1–25 kg, 450 mg; 25.1–32 kg, 600 mg; and 32.1–50 kg, 750 mg.**[45]				

1HP: 1 month of once-daily isoniazid and rifapentine

3HP: 3 months of once-weekly isoniazid and rifapentine

p3HP: 3HP given once a year for 2 years

3HR: 3 months of daily isoniazid and rifampin

4R: 4 months of daily rifampin

6H: 6 months of daily isoniazid

9H: 9 months of daily isoniazid

ACTG: AIDS Clinical Trials Group, U.S. National Institutes of Health (United States)

BMRC: British Medical Research Council

CIHR: Canadian Institutes of Health Research

DFID: Department for International Development (United Kingdom)

FDC: fixed-dose combination

FQ-R: fluoroquinolone-resistant tuberculosis

HIV: human immunodeficiency virus

IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health (United States)

KNCV: KNCV Tuberculosis Foundation (the Netherlands)

LTBI: latent tuberculosis infection

MDR-TB: multidrug-resistant tuberculosis

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

PK: pharmacokinetics

SA MRC: South African Medical Research Council

TB: tuberculosis

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

USAID: United States Agency for International Development

WHO: World Health Organization

The Pediatric TB Treatment Pipeline

PK and safety studies in children continue to progress, producing a steady flow of data (Tables 4 and 5). The translation of research and development gains into policy for children with TB is improving. In the 2019 *WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment*, the WHO recommends bedaquiline for use in children as young as six years old and delamanid for use in children as young as three years old. The guidance also includes updates to the weight-based dosing schedules for other second-line medicines for children (levofloxacin: 15–20 mg/kg; moxifloxacin: 10–15 mg/kg; linezolid: 10–15 mg/kg; clofazimine: 2–5 mg/kg; cycloserine: 15–20 mg/kg; isoniazid: 15–20 mg/kg).[46] However, target drug exposures continue to evolve.

Studies underway or recently completed in adults are evaluating how to optimize dosing for existing TB medicines, including rifampin, isoniazid, linezolid, and the fluoroquinolones.

Treatment-shortening regimens composed of existing TB medicines administered using new doses and/or new dosing schedules are under evaluation in adults, creating new target drug exposures and pediatric dosing and safety data gaps (Table 6). Additionally, mathematical modeling exercises have sounded an alarm that the doses established for the first-line TB medicines in children may produce suboptimal exposures linked to poor treatment response, especially in young and malnourished children.[47] These findings raise questions about the current approach to weight-based dosing (irrespective of age and nutritional status), suggest that a standalone rifampin pediatric formulation may be required to supplement dosing in certain children, and further erode the assumption that 'one size' can fit all children with TB.[48]

Continued investments in pediatric PK and safety studies, as well as rapid translation of findings into policy and practice, will be necessary for children to benefit from ongoing TB treatment optimization work and future TB medicines and regimens, especially as compounds with new mechanisms of action are beginning to enter phase II.[49]

Delays to the initiation and completion of pediatric PK studies, and the tentative approach to (and apparent lack of interest in) commercializing pediatric formulations of TB medicines, are lengthening access gaps between adults and young children (Figure 1). Pediatric PK and safety studies of bedaquiline opened to enrollment four years after the United States Food and Drug Administration (FDA) granted bedaquiline accelerated approval; Janssen estimates its pediatric study will be completed in 2025 (13 years after FDA approval). Five years after the European Medicines Agency (EMA) conditionally approved delamanid, Otsuka's PK and safety study finally completed enrollment, but the dose selected for children up to two years old resulted in suboptimal exposures; Otsuka is collaborating with the IMPAACT network on P2005, which offers an opportunity to refine delamanid dosing for young children. Pretomanid — a new drug in multiple phase III trials — was approved by the FDA in August 2019. The TB Alliance has developed a pediatric investigation plan for pretomanid, but investigations have yet to begin because the TB Alliance must first complete a semen substudy. Plans and timelines for the semen substudy remain unclear, though we have been reporting on this requirement since 2015.

TB disease severity and presentation are highly variable in children. Very young children (0 to <2 years old) more commonly develop disseminated TB, young children (2 to ≤12 years old) tend to have paucibacillary and noncavitary TB, and older children (>12 years old) often present with adult-like pulmonary disease. There is a need to determine whether good outcomes can be achieved in children with less-severe forms of TB using further simplified regimens and to optimize regimen composition, duration, and dosing for the more severe manifestations of TB disease also observed in children. Several efficacy studies underway or planned will evaluate whether it is possible to shorten and optimize treatment for drug-sensitive TB (DS-TB) and DR-TB and tuberculous meningitis (TBM) in children (Table 4). The advancement of such studies should serve as a further signal to the TB community regarding the importance of pediatric-specific interventions on TB.

Table 4. Ongoing and Planned TB Treatment Studies in Children

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
DRUG-SUSCEPTIBLE TB				
OptiRif Kids	Enrolling; results expected 2020	PK, safety, and dose optimization of rifampin for treatment of TB	HIV-negative infants and children 0–12 years old with TB	Unitaid (STEP-TB Project)
Higher doses of rifampin are being explored in adults in an effort to further improve treatment outcomes and shorten treatment, as the optimal dosing of rifampin was never established. At 20 mg/kg and 35 mg/kg, children achieved lower rifampin exposures than adults dosed at 35 mg/kg. Pediatric rifampin exposures and safety will be evaluated at 50 mg/kg and potentially higher doses.[50]				
SHINE CTRI/2017/07/009119	Enrollment complete; results expected 2020	Efficacy and safety of 4 vs. 6 months of treatment (using updated WHO dosing guideline-adjusted FLD FDCs) for nonsevere TB	HIV-positive or HIV-negative infants, children, and adolescents 0–16 years old with nonsevere TB	BMRC, DFID, Wellcome Trust
TBM-KIDS NCT02958709	Enrolling; results expected 2020	Efficacy and safety of high-dose rifampin ± levofloxacin for treatment of TBM	HIV-positive or HIV-negative infants and children 6 months to 12 years old with TBM	NICHD
SURE-TBM ISRCTN40829906	Planned	Efficacy and safety of high-dose rifampin, levofloxacin, and isoniazid with pyrazinamide for shortening treatment of TBM to 6 months	HIV-positive or HIV-negative infants, children, and adolescents 28 days to 15 years old with TBM	BMRC, DFID, NIHR, Wellcome Trust

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
CO-TREATMENT WITH ARVs				
IMPAACT P1106 NCT02383849	Enrolling; results expected 2023	PK and safety of rifampin and isoniazid with nevirapine or lopinavir/ritonavir	HIV-positive or HIV-negative low-birth-weight/ premature infants	NIAID, NICHD
Low-birth-weight, HIV-exposed infants given nevirapine dosed at 2 mg/kg daily for 14 days followed by 4 mg/kg daily safely achieved drug concentrations above the prophylaxis target. Isoniazid PK data were also collected and will be presented in 2019.[51] **Low- and normal-birth-weight newborns <3 months old living with HIV given 300/75 mg/m2 lopinavir/ritonavir twice daily safely achieved drug concentrations similar to those seen in adults. The FDA label for lopinavir/ritonavir only recommends use when >2 weeks postnatal age (time since birth) and >42 weeks post-conceptional age (gestational age plus time since birth). These data suggest that lopinavir/ritonavir can be safely and effectively used in newborns below these thresholds.[52]**				
IMPAACT P1101 NCT01751568	Enrolling; interim results presented (see below); final results expected 2020	PK and safety of raltegravir with rifampin-containing TB treatment	ARV-naive, HIV-positive infants, children and adolescents 4 weeks–12 years old with TB	NIAID, NICHD
A 12 mg/kg dose of raltegravir given twice daily safely achieved PK targets among HIV-positive children 2 to <6 years old and 6 to <12 years old on rifampin-based TB treatment. Cohort 3, which will evaluate this dosing approach in children 4 weeks to <2 years old is enrolling.[53,54]				
ODYSSEY NCT02259127	Enrollment complete; results expected 2020	Efficacy and safety of dolutegravir-based ART vs. standard of care	HIV-positive children and adolescents 6–18 years old starting first-line or switching to second-line ART, including children co-infected with TB	PENTA Foundation
Similar and appropriate dolutegravir PK profiles can be achieved in children weighing 20 to <25 kg using 50 mg film-coated tablets (the formulation given to adults) or 30 mg dispersible tablets.[55]				

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
DRUG-RESISTANT TB				
MDR-PK 1/ MDR-PK 2	**Results presented/ published (see below);** **MDR-PK 2 still enrolling; additional results expected 2018–2020**	**PK, safety, and dose optimization of SLDs for treatment of MDR-TB**	**HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or exposure to MDR-TB**	**NICHD, SA MRC**
Population PK models, combining PK data from multiple individuals, can predict and simulate how drugs behave in the body. Population PK models built using pediatric data from MDR-PK 1 and MDR-PK 2 determined that: ■ **dosing linezolid at 10–20 mg/kg achieved higher than expected exposures in children compared with target adult exposures achieved with 600 mg daily dosing. Adverse events were common and sometimes severe. Lower doses with the potential to approximate target exposures and reduce the occurrence and severity of adverse events should be evaluated in children.[56]** ■ **dosing levofloxacin at 15–20 mg/kg is safe and well tolerated but produces lower exposures in children compared with those in adults with the formulation studied (adult 250 mg tablets).[57,58]** ■ **dosing moxifloxacin at 7.5–10 mg/kg produces considerably lower exposures in children compared with those in adults, and the effect is worse in smaller children.[59]** ■ **dosing amikacin at 15–20 mg/kg produces maximum plasma concentrations at target levels for the majority of children.[60]** **A separate PK study that evaluated a new 100 mg levofloxacin dispersible tablet in children <5 years old who had a household contact with MDR-TB found that dosing levofloxacin at 15–25 mg/kg produced exposures in children that approximated those achieved in adults. Differences in bioavailability likely account for the higher exposures achieved with the 100 mg pediatric formulation relative to the 250 mg adult formulation. The adult formulation had 41 percent lower bioavailability than the pediatric formulation. Higher doses may be necessary when adult tablets are used.[61]** **MDR-TB treatment did not have any significant interaction with or effect on the PK of lopinavir/ritonavir in children with HIV and TB.[62]** **Analysis of ethionamide, PAS, high-dose isoniazid, and terizidone data is ongoing. Analysis of clofazimine data and of additional moxifloxacin and linezolid data are also expected.**				
232 NCT01856634	Enrollment complete; interim results presented (see below); final results expected 2019	PK and safety of delamanid; OBR for treatment of MDR-TB	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
Data on the PK and safety of delamanid available in children down to 3 years old informed a recommendation from the WHO extending the use of delamanid for the treatment of MDR-TB in adults to children 3 years and older. **Dosing recommendations for administering delamanid to children are as follows (1.5–3.8 mg/kg): 12–17 years old, 100 mg twice daily; 6–11 years old, 50 mg twice daily; 3–5 years old, 25 mg twice daily (using the pediatric dispersible tablet formulations).[63]**				

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
233 NCT01859923	Enrolling; final results expected 2020	Efficacy, safety, and PK of 6 months of delamanid; OBR for treatment of MDR-TB	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT P2005 NCT03141060	Enrolling; final results expected 2022	PK and safety of delamanid; all-oral OBR for treatment of MDR-TB	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, NICHD
JANSSEN C211 NCT02354014	Enrolling; final results expected 2025	PK and safety of bedaquiline; OBR for treatment of MDR-TB	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen
IMPAACT P1108 NCT02906007	Enrolling; final results expected 2023	PK and safety of bedaquiline; OBR for treatment of MDR-TB	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤5 years old will get pediatric formulation	NIAID, NICHD
Data on the PK and safety of bedaquiline available in children down to 6 years old informed a recommendation from the WHO extending the use of bedaquiline for the treatment of MDR-TB in adults to children 6 years and older. **Dosing recommendations for administering bedaquiline to children are as follows: 15–17 years old (and >5 years old and >29 kg), 400 mg daily for 2 weeks, then 200 mg thrice weekly; >5 years old and 15–29 kg, 200 mg daily for 2 weeks, then 100 mg thrice weekly.[64]**				
IMPAACT P2020	Protocol in development	Efficacy and safety of 6 months of bedaquiline, delamanid, and levofloxacin or clofazimine, plus linezolid for the first 8 weeks for treatment of RR-TB, with or without FQ-resistance	HIV-positive or HIV-negative infants, children, and adolescents <15 years old with RR-TB, with or without FQ-resistance	NIAID, NICHD

Table 5. Recently Completed TB Treatment Studies in Children

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
DRUG-SENSITIVE TB				
Treat Infant TB	Results published 2016 (see below)	PK of FLDs using updated WHO dosing guidelines for treatment of TB	HIV-positive or HIV-negative infants <12 months old with TB	Unitaid (STEP-TB Project)
When administered according to WHO-recommended pediatric weight-based doses, pyrazinamide and isoniazid achieved drug exposures in infants that are comparable to those in adults. Exposures of rifampin and ethambutol were lower than those achieved in adults. HIV-positive infants taking ARVs (abacavir, lamivudine, and lopinavir/ritonavir) achieved lower pyrazinamide and ethambutol exposures than did HIV-negative infants. Whether dosing adjustments are necessary requires further evaluation.[65]				
PHATISA	Results published 2015 (see below)	PK of FLDs using updated WHO dosing guidelines for treatment of TB	HIV-positive or HIV-negative infants ≤10 years old with TB	NIH, HHMI
When administered according to WHO-recommended pediatric weight-based doses, drug concentrations for isoniazid, rifampin, pyrazinamide, and ethambutol were below target therapeutic concentrations in most children. Whether drug exposure targets linked with good outcomes in adults are necessary to achieve good outcomes in children, especially considering differences in bacterial burden and severity and location of disease, requires investigation.[66]				
PK-PTBHIV01 NCT01687504	Results published 2017–2018 (see below)	PK of FLDs using updated WHO dosing guidelines for treatment of TB	HIV-positive or HIV-negative children 3 months to 14 years old with TB	NICHD
Children treated according to WHO dosing guidelines had low rifampin and ethambutol exposures. Children with HIV and TB had significantly lower plasma exposure and a higher apparent oral clearance of rifampin, pyrazinamide, and ethambutol. Children with both HIV and TB were not yet started on antiretroviral drugs at the time of pharmacokinetic sampling, so observed lower exposures could be due to impaired absorption and/or enhanced metabolism or excretion. Whether children, especially children in the lower weight bands and/or who have HIV and TB, need higher doses requires further investigation.[67,68,69] **A population PK model of the first-line medicines in children determined that young children had low pyrazinamide and ethambutol exposures; isoniazid exposures were low in rapid acetylators. Age, weight, and genotype helped to account for interpatient variability in exposures. Simulated doses found that lower limits of exposures associated with long-term outcomes in adults were attainable in children at higher doses than are currently recommended by the WHO: rifampin: ≥30 mg/kg (10–20 mg/kg); isoniazid: 12–18 mg/kg (10–15 mg/kg) for rapid acetylators; pyrazinamide: 25–70 mg/kg (30–40 mg/kg); and ethambutol: 25–60 mg/kg (15–25 mg/kg). Higher doses of pyrazinamide and ethambutol should be tested in children and evaluated for safety.[70]**				

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
CO-TREATMENT WITH ARVs				
DATiC NCT01637558	Results published 2016–2019 (see below)	PK of FLDs using updated WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine	HIV-positive or HIV-negative infants, children, and adolescents 1 month to 12 years old with TB	NICHD
Children achieved isoniazid and pyrazinamide drug exposures comparable to those in adults. Ethambutol exposures were lower in children. Exposures of rifampin were variable, with only 17 percent of children achieving adult exposures and reduced exposures in the lowest and highest weight categories; the quality and formulation effect of available rifampin suspensions may have affected the PK of rifampin, contributing to the lower exposures observed.[71,72,73,74,75] **The proposed novel dosing strategy of lopinavir/ritonavir (4:1) every 8 hours when co-administered with rifampin (thought to be easier to administer with available formulations of lopinavir/ritonavir) failed to achieve adequate lopinavir concentrations in 4 of 11 participants (36 percent). Dosing every 8 hours is not supported over the currently recommended dosing strategy of lopinavir/ritonavir (1:1) twice daily when co-administered with rifampin (see HIVPED001).[76]**				
PK-TBHIV02 NCT01699633	Results expected 2019	PK and safety of nevirapine with rifampin-containing TB treatment	HIV-positive children 3 months to 3 years old with TB	NICHD
Publication submitted to *Antimicrobial Agents and Chemotherapy*.				
IMPAACT P1070 NCT00802802	Results presented 2019 (see below)	PK and safety of efavirenz with rifampin-containing TB treatment	HIV-positive children 3 months to <3 years old with or without TB	NIAID, NICHD
Adequate efavirenz exposures and virologic suppression were safely achieved using genotype-directed dosing in HIV-positive children <2 years old.[77] Children with HIV and fast metabolism of drugs processed by the cytochrome P450 2B6 enzyme (encoded by the CYP2B6 gene) require higher doses of efavirenz (50 mg/kg). Children with HIV with slow CYP2B6 metabolism can achieve target efavirenz concentrations when given just 25 percent (12.5 mg/kg) of the dose administered to children with fast metabolism. **Increasing the dose of efavirenz (by 30 percent; 65 mg/kg) for children with HIV and TB was safe and produced therapeutic concentrations and good virologic outcomes. However, PK modeling suggests that appropriate efavirenz exposures can be achieved in children <2 years old receiving TB treatment without this additional dose adjustment. More data are required to confirm appropriate dosing for children 2 to 3 years old.[78,79,80]**				
PK-PTBHIV03 NCT01704144	Results published 2018 (see below)	PK and safety of efavirenz with rifampin-containing TB treatment	HIV-positive children and adolescents 3–14 years old with TB	NICHD
Children with HIV and TB had significantly lower efavirenz plasma exposure and trough concentrations than children with HIV alone. The proportion of children with subtherapeutic efavirenz exposure was higher among children with HIV and TB (47.4 vs. 17.6 percent). Studies to examine virologic outcomes in children with HIV and TB on efavirenz are necessary.[81] **A population PK model determined that first-line TB medicines reduced efavirenz clearance (increased plasma exposure) but led to similar PK parameters in HIV-positive children with and without TB. These findings suggest that efavirenz dose modifications are not necessary for HIV-positive children receiving TB treatment.[82]**				

Study/Regimen	Status	Regimen	Population(s)	Funder(s)
HIVPED001 NCT02348177	Results presented 2017 (see below)	PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment	HIV-positive infants and children with TB weighing 3–15 kg; DNDi developing standalone ritonavir booster formulation	DNDi, AFD, UBS Optimus Foundation, MSF
Exposures following superboosted doses of lopinavir/ritonavir (1:1) with rifampin were noninferior to exposures following standard doses of lopinavir/ritonavir (4:1) without rifampin. Virologic efficacy and safety were also comparable.83 These results led to strengthened WHO recommendations to use superboosting in children with HIV and TB on lopinavir/ritonavir.84 Safe and effective superboosting could be improved by replacing liquid formulations with new solid formulations of lopinavir/ritonavir (40 mg/10 mg mini-tablets and granules of lopinavir/ritonavir and 100 mg sachets of ritonavir). The effect of increased doses of rifampin on super-boosted lopinavir drug concentrations requires evaluation.[85]				
DRUG-RESISTANT TB				
TASK-002 (BDQ Crush Study)	Results published 2018 (see below)	Bioequivalence of bedaquiline 400 mg tablets administered whole or crushed and suspended in water	Healthy adult volunteers	NIAID, NICHD
There was no significant difference in the bioavailability of bedaquiline administered whole or crushed and suspended in water, and the suspension was well tolerated; predefined bioequivalence criteria were also fulfilled. This suggests that the currently available formulation of bedaquiline could be used to treat children to bridge the gap between when pediatric dosing and safety have been established and when the pediatric dispersible formulation will be routinely available.[86]				

AFD: French Development Agency

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 Initiative

FDC: fixed-dose combination

FLD: first-line drug

FQ-R: fluoroquinolone-resistant tuberculosis

HHMI: Howard Hughes Medical Institute

HIV: human immunodeficiency virus

IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health

LTBI: latent tuberculosis infection

MDR-TB: multidrug-resistant tuberculosis

MSF: Médecins Sans Frontières

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

NIH: U.S. National Institutes of Health

NIHR: National Institute for Health Research (United Kingdom)

OBR: optimized background regimen

PAS: Para-aminosalicylic acid

PENTA: Pediatric European Network for Treatment of AIDS

PK: pharmacokinetics

Pre-XDR TB: pre-extensively drug-resistant tuberculosis

RR-TB: rifampin-resistant tuberculosis

SA MRC: South African Medical Research Council

SLD: second-line drug

TB: tuberculosis

TBM: tuberculous meningitis

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

TST: tuberculin skin test

UBS: Union Bank of Switzerland

WHO: World Health Organization

XDR-TB: extensively drug-resistant tuberculosis

Table 6. Pediatric TB Pharmacokinetic and Safety Data Gaps

Drug	**Current Adult Dose/Dosing Schedule Established or Under Investigation** [Relevant Pediatric Studies]	**New Adult Dose/Dosing Schedule Under Investigation or Planned** [Relevant Adult Studies]	**Anticipated Pediatric PK Research Gaps**
Bedaquiline	400 mg daily for 2 weeks, then 200 mg thrice weekly [P1108; C211]	200 mg daily for 8 weeks, then 100 mg daily [SimpliciTB, NCT03338621; ZeNix, NCT03086486]	Lower bedaquiline doses administered daily
Delamanid	200 mg daily [C212/213; P2003B]		
Clofazimine	100 mg daily [MDR PK; P2020]	200 mg daily for 8 weeks, then 100 mg daily [endTB, NCT02754765; endTB-Q, NCT03896685]	Loading clofazimine doses
Isoniaizid (H)	300–600 mg daily [MDR PK]	500–1000 mg daily [NEXT, NCT02454205; A5312, NCT01936831]	Higher isoniazid doses
Levofloxacin	11–14 mg/kg daily [MDR PK; TB CHAMP]	17–20 mg/kg daily [TBTC S32, NCT01918397]	Higher levofloxacin doses
Linezolid	300–600 mg daily [MDR PK; P2020]	600–1200 mg daily [ZeNix, NCT03086486]	Higher linezolid doses
Moxifloxacin	400 mg daily [MDR PK]	400–800mg daily [STREAM, NCT02409290]	Higher moxifloxacin doses
Pretomanid	200 mg daily [planned – TB Alliance]		
Rifampin (R)	10–35+ mg/kg daily [OptiRif Kids]	10–55+ mg/kg daily [HR, NCT01392911]	Higher rifampin doses
Rifapentine (P)	P:900 mg/H:900 mg once weekly P:600 mg/H:300 mg daily [TBTC S35; CS 5019]	P:600 mg daily [TBTC S37, NCT03474029] P:1200 mg daily [TBTC S31/A5349, NCT02410772; TRUNCATE-TB, NCT03474198]	Higher rifapentine doses administered daily

Table 7. Pediatric TB Formulations Available or Close to Market

Drug	Current Regimen/ Indication	Pediatric Formulation(s)	Status	Sponsor	Current Gap(s)	Future Regimen/ Indication
Bedaquiline	DR-TB	20 mg DT	Trial formulation	Janssen	PK/ safety data in children <6 years old	DS-TB [SimpliciTB, NCT03338621]
Clofazimine	DR-TB	50 mg capsule	SRA	Novartis		
		50 mg DT	GF ERP	Macleods		
Cycloserine	DR-TB	125 mg capsule	WHO PQ	Macleods		
Delamanid	DR-TB	5, 25 mg DT	Trial formulation	Otsuka	PK/ safety data in children <3 years old	TPT [A5300/P2003; NCT03568383]
Ethambutol	DS-TB/ DR-TB	100 mg DT	WHO PQ	Macleods		
Ethionamide	DR-TB	125 mg DT	WHO PQ	Macleods		
			WHO PQ	Micro Labs		
Isoniazid	6H for TPT; HD for DR-TB	100 mg DT	under review	Macleods		
			under review	Micro Labs		
Levofloxacin	DR-TB/ TPT	100 mg DT	WHO PQ	Macleods		
			GF ERP	Micro Labs		
Linezolid	DR-TB	150 mg DT	In development	Macleods		
		100 mg/5 ml granules for oral suspension	SRA	Pharmacia UK		
Moxifloxacin	DR-TB	100 mg DT	WHO PQ	Macleods		DS-TB [TBTC S31/ A5349, NCT02410772
			WHO PQ	Micro Labs		
Pas	DR-TB	Granules	WHO PQ	Macleods		
		Granules	SRA	Jacobus		
		Powder oral solution	SRA/ WHO PQ	OlainFarm		
Pretomanid	DR-TB	Unknown	Trial formulation under development	TB Alliance	PK/ safety data in children of all ages	DS-TB [SimpliciTB, NCT03338621]
Pyrazinamide	DS-TB/ DR-TB	150 mg DT	WHO PQ	Macleods		
Rifampin	4R for TPT	None	NA	NA	Standalone R for prevention	
	HRZ for DS-TB	50/75/150 mg DT	WHO PQ	Macleods	Standalone R to top up dose	
	HR for DS-TB/ TPT	50/75 mg DT	WHO PQ	Macleods		
			GF ERP	Lupin		
Rifapentine	3HP for TPT	150/150 mg DT; 100 mg DT	Trial formulation	Sanofi	PK/ safety data in children <2 years old	HD P daily for DS-TB [TBTC S31/A5349, NCT02410772]
	1HP for TPT	150/150 mg DT; 100 mg DT	Trial formulation	Sanofi	PK/ safety data to inform daily P dose	

1HP: 1 month of once-daily isoniazid and rifapentine

3HP: 3 months of once-daily isoniazid and rifapentine

4R: 4 months of daily rifampin 6H: 6 months of daily isoniazid

DR-TB: drug-resistant TB

DS-TB: drug-sensitive TB

DT: dispersible tablet

GF ERP: Global Fund Expert Review Panel

HRZ: isoniazid, rifampin, pyrazinamide

MDR-TB: multidrug-resistant tuberculosis

PK: pharmacokinetics

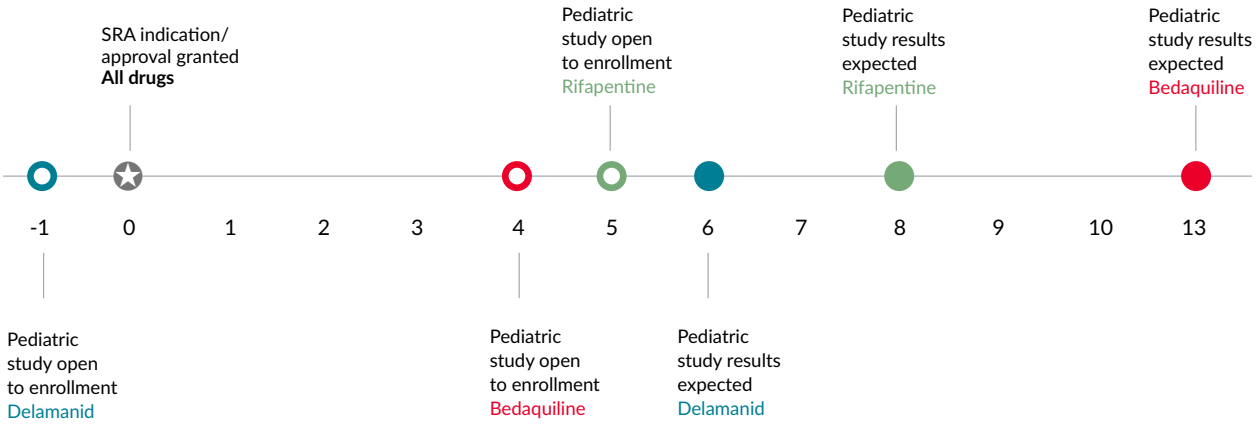
PQ: Pre-qualification

SRA: Stringent Regulatory Authority

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

WHO: World Health Organization

Figure 1. Years From Approval in Adults to Expected Final Pediatric Research Results



	Rifapentine	Delamanid	Bedaquiline	Pretomanid
SRA indication/ approval granted	2014	2014	2012	2019
Pediatric study open to enrollment	2019	2013	2016	
Pediatric study results expected	2022	2020	2025	

Endnotes

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