Chapter 15

Tuberculosis in children and adolescents: a forgotten group in a forgotten disease

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Cite as: López-Varela E, Munyangaju I, Chabala C, *et al.* Tuberculosis in children and adolescents: a forgotten group in a forgotten disease. *In:* García-Basteiro AL, Öner Eyüboğlu F, Rangaka MX, eds. The Challenge of Tuberculosis in the 21st Century (ERS Monograph). Sheffield, European Respiratory Society, 2023; pp. 210–234 [https://doi.org/10.1183/2312508X.10025322].

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TB in children and adolescents is associated with high morbidity and mortality. However, new guidelines, including shorter treatment regimens, can help address some of the unique challenges faced by this population. https://bit.ly/ERSM101

 Print ISBN: 978-1-84984-169-6. Online ISBN: 978-1-84984-170-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Despite being both treatable and preventable, TB in children and adolescents continues to cause substantial mortality and morbidity in high-incidence settings. Major challenges include missed opportunities for TB prevention and poor case detection, particularly in young children. Although historically neglected, recent developments, including the 2022 WHO child and adolescent TB guidelines, represent important milestones in improving TB prevention and care in this population. The guidelines include the use of treatment decision algorithms, shorter treatment regimens, and TPT for both drug-susceptible and DR-TB, as well as steps to address the unique needs of adolescents. Closing persistent policy-practice gaps will be necessary to ensure that these new developments are implemented effectively. This chapter emphasises the need for continued efforts to prevent and control TB in children and adolescents, which will require a multifaceted approach involving governments, health systems and communities.

Introduction

Childhood TB has historically been a near-invisible part of the global TB epidemic. This can be attributed to several factors, including a reliance on sputum smear microscopy for diagnosis. Only a few children were historically confirmed microbiologically, leading to poor quantification of the disease burden. Childhood TB lags behind progress in adults in our understanding of disease burden and also in research and development of diagnostics and treatments. Yet children are particularly vulnerable to developing TB disease after exposure, which can progress to severe forms of the disease, including TB meningitis (TBM). Older

children and adolescents can transmit *Mycobacterium tuberculosis* and so contribute to disease propagation, and children infected with *M. tuberculosis* provide a reservoir for future disease. Thus, addressing child and adolescent TB is essential in the fight towards TB elimination.

After years of neglect, child and adolescent TB is finally gaining more attention in global TB efforts. A key focus of the WHO's global End TB Strategy is to end the TB epidemic by 2030, including diagnosing and treating at least 90% of children with TB [1]. At the 2018 United Nations High-Level Meeting, a global target was also set to diagnose and treat 3.5 million children with TB by 2022. By the end of 2021, only 1.9 million (54% of the target) had been treated in the years 2018–2021. A target was also set to offer TPT to 4 million children <5 years of age who are at risk of developing TB by 2022 [2]. However, over the period 2018–2021, only 1.6 million children (40% of the target) had been offered TPT.

In this chapter, we will discuss the diagnosis and treatment of TB in children and will highlight recent developments. We will end by identifying research priorities in the field.

Epidemiology and natural history

Burden of paediatric TB

TB in children (<15 years) represents 11% of the global TB burden, but this figure can be higher in high-TB-burden countries. Typically, high-TB-burden countries have 40–50% of their population aged <15 years, and given the high frequency of exposure to *M. tuberculosis*, children are more likely to be exposed at a younger age, when TB progression is more likely [3]. It was only in 2012 that the WHO produced the first child-specific estimates of incidence and mortality for child TB [4]. Initially, the WHO used burden estimation methodology similar to that used in adults with the same estimated case detection rate. However, in recent years, more sophisticated ensemble modelling approaches have been used [5].

Modelling studies have estimated that 67 million children (<15 years) were infected with *M. tuberculosis* worldwide in 2014 [6], and the 2022 WHO TB report estimated that, of these, 1.2 million developed TB disease in 2021 [2]. Over half of these children are not reported, with the highest case-detection gap (69%) in children <5 years [7]. This is mainly a result of continuing limitations in available screening and diagnostic measures for children exposed to TB, health worker capacity and their confidence to diagnose children with TB, the paucibacillary nature of the disease in this population, challenges in accessing health services [8, 9] and recently the COVID-19 pandemic [2, 10]. In 2021, an estimated 209 000 children <15 years of age died of TB, and modelling studies suggest that 96% of child TB deaths occur in children who were undiagnosed. Most of these deaths occur in children <5 years, an age with a higher risk of severe disease and mortality, and the group with the most profound diagnostic challenges [2, 11, 12]. Estimates for MDR-TB (disease caused by *M. tuberculosis* resistant to at least isoniazid and rifampicin) suggest that ~30 000 children develop the disease each year [6, 13]. Only one-fifth of these are diagnosed, treated and reported to the WHO [2].

Reliable estimates of childhood TB disease burden are difficult to make due to diagnostic limitations and deficient recording and reporting, as well as limitations in the method used to calculate estimates from the number of reported cases [14]. Suggested best practices for improving reporting and recording include individual-level participant electronic registries, integration of TB services in child health services, integration of databases at the multiple entry points and engagement of different sectors involved in TB care (private sector and nongovernmental organisations) [15–18].

Natural history and spectrum of disease

Children become infected with *M. tuberculosis* through exposure to an infectious TB source case. It was previously assumed that this was usually someone in their immediate or extended household. However, it is increasingly recognised that substantial transmission occurs in the community [8].

Following infection, the risk of progressing to TB disease is highest in infants and children <5 years of age due to an immune system that is relatively ineffective at controlling *M. tuberculosis* replication. Disease progression can occur rapidly (within a few weeks), but the risk remains high for up to 2 years after infection [7, 12, 13]. The risk falls to a nadir in children between 5 and <10 years and increases again in adolescents. Adolescent females have a higher incidence than males, but the risk inverts in adulthood [19]. Many factors contribute to this, such as hormonal changes that affect the immune system during puberty, viral coinfections, and sex inequality in access to healthcare and health-seeking behaviour (which has also been linked to increased mortality) [19].

The spectrum of disease in children is diverse and age dependent (see figure 4 in chapter 14 of this *Monograph* [20]). Most young children present with minimal disease limited to the intrathoracic lymph nodes, which is often subclinical, paucibacillary and rarely transmissible. Some children, however, can present with extensive disease, including parenchymal pathology, or endobronchial disease, which can result from local complications of intrathoracic lymph-node disease. In young children, EPTB, such as miliary TB or TBM, is also more common. With the onset of puberty, TB disease phenotypes switch to adult-type TB, which is characterised by cavities, increased bacillary loads and higher infectiousness [21].

Children living with HIV have an 8-fold increased risk of TB, a risk that remains elevated, even with a relatively high $CD4^+$ count and/or a low or undetectable viral load [22, 23]. It is common for immunocompromised children and adolescents, regardless of their age, to present with more severe forms of disease, similar to those of younger children.

Decision making

Active case finding

TB is both preventable and curable. In order to provide appropriate prevention or treatment for children with infection or disease, the first step is to correctly identify and diagnose them. For this, active or passive case-finding strategies can be used. In passive case finding, TB is identified in an often-symptomatic child or adolescent whose clinical condition has prompted their visit to a health facility. Active case finding involves the practice of evaluating individuals at high risk for TB who have not been brought due to clinical concerns.

Active case detection is necessary to close the large case-detection gap characterised by paediatric TB [24]. The WHO's End TB Strategy includes this intervention as a core component to eradicate TB. It serves several goals. First, early TB detection serves to minimise avoidable delays, thus reducing mortality and improving outcomes. Second, early detection reduces TB transmission by shortening the duration of infectiousness. Third, TPT prevents new TB cases. According to the WHO, active case-finding approaches are indicated for several at-risk groups, with implementation considerations varying based on the context and disease burden (box 1) [26, 27].

Decision making for TPT

To make TPT decisions, TBI testing (TST or IGRA) is recommended by the WHO whenever feasible (especially in children >5 years of age) but is not a requirement. TBI tests, although imperfect, have a high positive predictive value when applied to children at high risk of TBI. The

 https://doi.org/10.1183/2312508X.10025322

BOX 1 WHO recommendations for active screening and TPT

Children and adolescents living with HIV as part of the comprehensive HIV care package[#]:
- <12 months with history of contact with a person with TB and in whom TB disease has been excluded
- >12 months and living in a high-TB-burden setting, in whom TB disease has been excluded, and regardless of history of TB contact
- All children who have completed TB treatment

Children and adolescents, irrespective of HIV status, who are household contacts of a bacteriologically confirmed PTB case, in whom TB disease has been excluded

Children who are candidates for anti-TNF treatment, dialysis, or organ or haematological transplant, or who have silicosis

Children and adolescents who are immigrants from high-TB-burden countries, are homeless, or who use drugs or are in prison

[#]: all children and adolescents living with HIV regardless of ART status should be screened for TB at every attendance using the following symptom screen: (any) cough, fever, poor weight gain or close contact with a person with TB. If they have any one of these symptoms, they should be investigated for TB. Data from [25].

TST has the advantage of being inexpensive and not requiring a laboratory infrastructure. However, due to overlap with non-*M. tuberculosis* antigens (including those found in the BCG), specificity is lower than for IGRA, especially in younger children. It is also a test that requires two patient visits. Newer TB-specific skin tests have been developed and are now recommended by the WHO [28]. IGRA testing is more expensive and requires a laboratory, but only requires one patient visit and has improved specificity compared with a conventional TST. In reality, none of these tests is widely available in low-resource settings, and the WHO has provided decision algorithms that do not rely on TBI tests to guide treatment decisions for children being considered for TPT (figure 1).

Decision making in children and adolescents with presumptive TB

To diagnose a child or adolescent with TB disease, the first step is to decide if they may have presumptive TB. This screening process (whether active or passive) serves to exclude children and adolescents at low risk of TB, thereby focusing diagnostic tools on those with a higher risk of disease. The WHO defines someone as having presumptive TB if they have unremitting symptoms lasting >2 weeks (any one of cough, fever, not eating well or anorexia, weight loss or failure to thrive, fatigue, reduced playfulness or decreased activity).

Confirmed and clinically diagnosed TB disease

Once a child or adolescent has been identified as having presumptive TB, a decision must then be made as to whether to start TB disease treatment or not. To inform this decision, the traditional approach is to take a full history, carry out a clinical examination, conduct host immune tests if relevant, obtain samples for microbiological analysis and complete imaging (table 1). TB disease is confirmed if a microbiological test is positive for *M. tuberculosis*, but due to the paucibacillary nature of child TB, most younger children will not have confirmed disease. As children get older and enter adolescence, the proportion with confirmed disease increases. The confirmation rate increases incrementally if more samples are sent for microbiological testing. Those who are identified with TB disease without microbiological confirmation are described as having clinically diagnosed TB disease. The health worker may prescribe antibiotics to the child if they are concerned about TB but do not believe they have sufficient evidence for TB treatment. Symptoms, signs and radiology often resolve due to time or antibiotic treatment for non-TB causes. If the features persist after a couple of weeks and after the antibiotics, the probability of

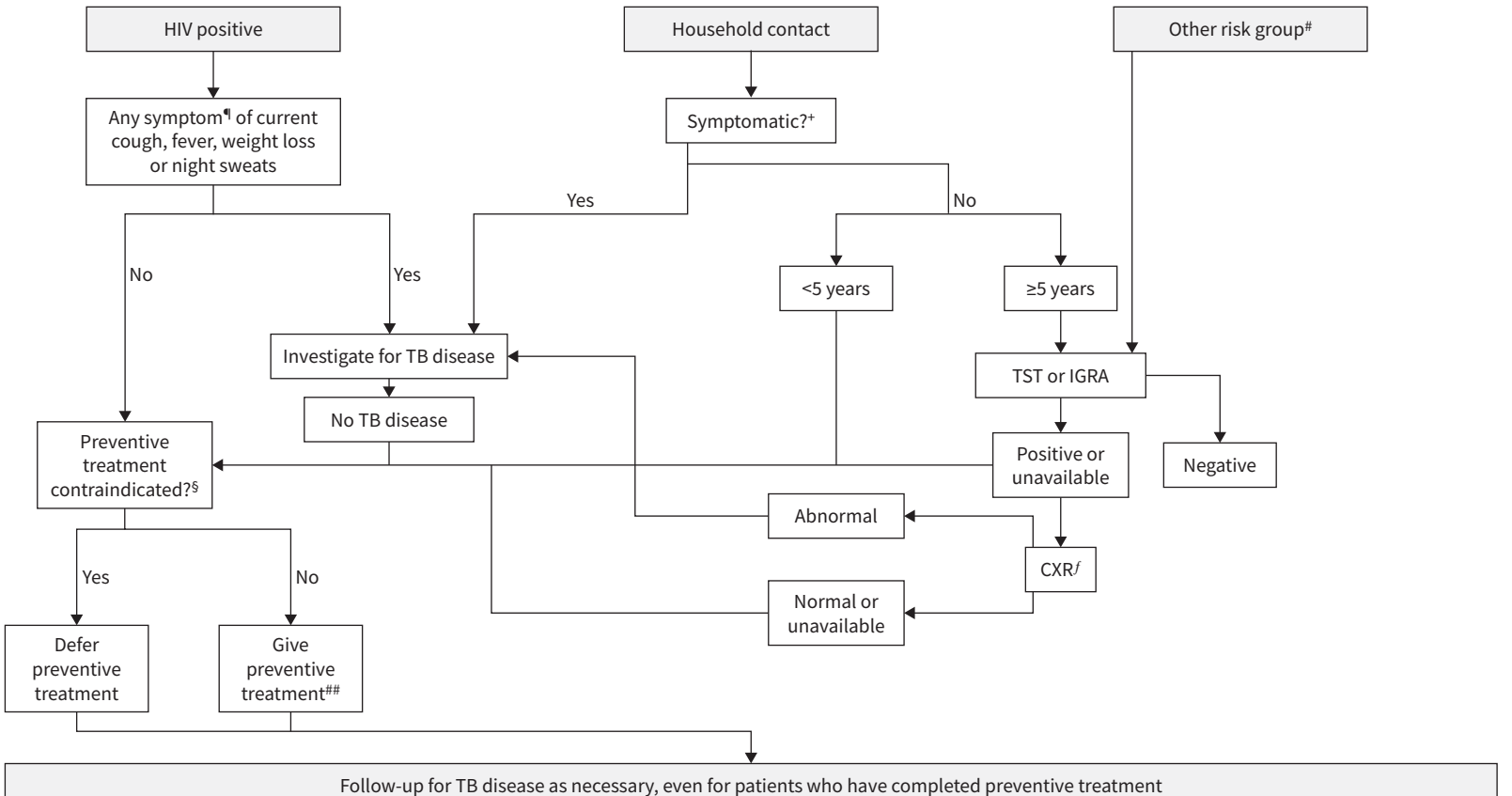

FIGURE 1 Legend overleaf.

https://doi.org/10.1183/2312508X.10025322

FIGURE 1 Algorithm for TBI testing and TPT in children and adolescents. [#]: including silicosis, dialysis, anti-TNF treatment, preparation for transplantation and other risks in national guidelines. People in this category should also have TB disease ruled out if they have suggestive clinical manifestations. [¶]: if aged <10 years, any one of a current cough, fever, history of contact with TB, reported or confirmed weight loss of >5% since the last visit, growth curve flattening or weight-for-age below −2 Z-scores. Asymptomatic infants aged <1 year living with HIV are treated for TBI only if they are household contacts of a person with TB. A TST or IGRA may identify PLHIV who will benefit most from TPT. CXR may be used in PLHIV on ART before starting TPT. [+]: any one of cough, fever, night sweats, haemoptysis, weight loss, chest pain, shortness of breath or fatigue. Children aged <5 years should not have anorexia, failure to thrive, not eating well, and decreased activity or playfulness to be considered asymptomatic. [§]: including acute or chronic hepatitis, peripheral neuropathy (if isoniazid is used) and regular heavy alcohol consumption. Pregnancy and a previous history of TB are not contraindications. [ƒ]: CXR may have been carried out earlier as part of intensified case finding. [##]: regimen chosen based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity, availability and preferences. Reproduced and modified from [27] with permission.

TB increases. Care must be taken when using time (with or without antibiotics) to assist in treatment decision making as it can delay the initiation of appropriate treatment. In most instances, a treatment delay for those with TB is not dangerous but caution must be exercised in young children (<2 years), those living with HIV, those who are malnourished, and any child with symptoms or signs of EPTB (other than isolated cervical lymphadenopathy). In cases of clinically diagnosed TB, it is important to continue assessing the child with consideration for other diagnoses, even after starting TB treatment. Children with presumed or confirmed TB should be tested for HIV, unless their status is already known. When a decision is made to treat a child for TB, it is also important to evaluate the severity of disease. CXR can help to make this assessment, but even in the absence of CXR, nonsevere disease can be defined as a child who does not have sputum smear-positive microscopy or a high bacillary burden using the Xpert MTB/RIF (or Xpert MTB/RIF Ultra) assay from a respiratory sample, has mild symptoms not requiring hospitalisation and in whom symptoms have completely resolved after 1 month of treatment [27].

Radiology

In children and adolescents, CXRs are commonly used to diagnose TB. Anteroposterior films are used in younger (<5 years) children and posteroanterior films are used in older children. A lateral image can be of great benefit in visualising hilar lymph nodes. A systematic approach should always be used when interpreting a paediatric CXR (figure 2). CXRs with abnormal findings should be evaluated for the presence of TB-specific features: hilar lymphadenopathy, airways compression, a miliary picture, large pleural effusion and cavities (figure 3). A patient with one of these features is likely to have TB, but their absence does not rule out TB. Abnormal features, such as opacification/consolidation, are consistent with TB as well as with other diseases. CXR can also be used to stratify treatment based on disease severity. Recent revisions to the *Diagnostic CXR Atlas for TB in Children* provide frontline health workers with valuable guidance [29]. CXRs have been evaluated extensively for adults using artificial intelligence, and the WHO now recommends their use as an alternative to human interpretation for screening and triage for TB in those >15 years of age [30]. There is now increasing work being done in this area for children and younger adolescents, but conclusive performance has not been determined. Lung, mediastinal and focused assessment with sonography for HIV/TB ultrasound imaging has also been explored in the last few years. In some settings where CXR is not available, point-of-care ultrasound may be a useful radiation-free, inexpensive alternative with lower inter-reader variation than CXR [31].

Treatment decision algorithms

Treatment decision algorithms (TDAs) have been used for decades to evaluate children with presumptive TB. An assessment of TB disease risk is based on history, examination,

TABLE 1 Diagnostic approaches in children

History	Symptoms: chronic, unremitting symptoms including cough, weight loss (or failure to put on weight as expected), fever, reduced playfulness: Nonspecific, more atypical (even acute) with immature/impaired immunity (infants/younger children or HIV/malnourished) Initial children of CNS are subtle and nonspecific History of exposure to an individual with infectious PTB: Less valuable as children grow older (more sources of contacts) Challenging; often, the index case is still undiagnosed (importance of reverse contact tracing) Specific symptoms locating disease to the site of possible EPTB
Examination	Weight loss or failure to gain weight appropriately (check curves) General: cachectic, lethargic PTB: coughing, wheezing, difficulty breathing, haemoptysis (a rare and late sign, generally seen only in adolescents), crackles or wheeze on auscultation Signs of EPTB dependent on site of disease
Immune tests	IGRA, TST and novel TST: These tests demonstrate immunological sensitisation to *M. tuberculosis* and do not discriminate TBI from TB disease (they do not indicate viable bacilli, only previous exposure); however, in a child or adolescent who has symptoms and signs that could be consistent with TB but also consistent with another diagnosis, a positive IGRA/TST may suggest an increased probability that their symptoms/signs are due to TB Conversion period of up to 3 months to become positive following infection TST has low specificity due to false positives for BCG and NTM; requires two visits (often with need for boosting at 8 weeks) IGRA requires laboratory infrastructure, phlebotomy (4 mL) and is expensive False negatives in young infants and with immunosuppression, severe malnutrition and severe TB Novel TST has better specificity than original TST but still requires two visits and has imperfect sensitivity
Microbiology	Sample collection: Respiratory samples include expectorated sputum, induced sputum, nasopharyngeal aspirates, gastric aspirates or washings, and stool samples (stool detects *M. tuberculosis* from both abdominal TB and from PTB that has been coughed up and swallowed; automated processing systems have been developed) Ideally, more than one and diverse; extrapulmonary samples might include cerebrospinal fluid to evaluate for TB meningitis, lymph-node aspiration biopsy samples for lymph-node disease, urine samples for renal or bladder TB, peritoneal fluid, biopsy samples from bone or joint samples Sample processing: Smear microscopy: a sample of sputum is smeared onto a microscope slide, stained with Ziehl–Neelsen stain (conventional) or auramine (fluorescence) and visualised under a microscope to detect *M. tuberculosis*; this test is cheap and fast but is associated with poor sensitivity, particularly in those with paucibacillary disease, and has poor specificity with NTM Mycobacterial culture can be on solid or liquid medium and is the most sensitive test to identify *M. tuberculosis* but is more expensive than a smear or NAAT, and commonly takes many days/weeks for a culture to be positive; compared with solid culture, liquid culture is more expensive and has higher contamination rates but is more sensitive; once cultured, either phenotypic or genotypic DST can be carried out

Continued

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TABLE 1 Continued

	NAATs involve PCR replication of *M. tuberculosis* DNA allowing detection of *M. tuberculosis* as well as mutations associated with drug resistance and can be carried out on clinical specimens or cultured samples; Xpert TBM/RIF and Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, USA) are widely used tests that identify rifampicin resistance, and Truenat MTB and MTB Plus (Molbio Diagnosis, Goa, India) are additional endorsed NAATs; line probe assays are also able to detect a wider range of drug-resistance mutations WGS sequences the entire *M. tuberculosis* genome and can detect all mutations associated with drug resistance but is currently expensive and largely unavailable outside research studies in high-TB-burden settings General principles: Should be attempted before treatment initiation, although should not delay treatment initiation (particularly of severe forms, including TBM) Obtaining respiratory samples is still valuable in EPTB with a normal CXR as the lung is usually the entry point Challenges exist in collecting samples in high-TB-burden settings (*i.e.* availability of equipment for sputum induction, ability to rapidly transport specimens, and adequate laboratory facilities, equipment and trained staff)
***M. tuberculosis* antigen**	Lipoarabinomannan in urine: Recommended by the WHO for child presumptive TB cases, living with HIV Suboptimal sensitivity and specificity Potentially useful additional test as part of a diagnostic approach
Radiology	CXR: Benefits include wide availability, low cost and ease of testing Challenges include imperfect sensitivity and specificity and inconsistent interpretation Computer-based interpretation is being developed for children <15 years of age Ultrasound: Can be used as a point-of-care test No radiation High intra- and inter-reader variability Limited experience in the diagnosis of TB in children CT and MRI scanning: Best visualisation of intrathoracic pathology, including lymph nodes Expensive and largely unavailable in high-TB-burden settings Large radiation dosage for CT Frequently requires sedation or anaesthetic for younger children
Novel biomarkers	Transcriptomic and proteomic biosignatures: Ability to distinguish confirmed TB from other diseases in research studies with high performance Expensive and not commercially available Unknown performance in real-world settings May have a place as part of a diagnostic algorithm

CNS: central nervous system; NTM: nontuberculous mycobacteria; *M. tuberculosis*: *Mycobacterium tuberculosis*; NAAT: nucleic acid amplification test; TBM: tuberculous meningitis; CT: computed tomography; MRI: magnetic resonance imaging.

microbiology and radiology results. Above a certain risk threshold, treatment initiation is advised. Using these tools, health workers at lower levels of healthcare and with less experience and training can start children on TB treatment. Until recently, most TDAs were developed using expert opinion. In 2021, the WHO commissioned a meta-analysis of individual participant data for their 2022 guidelines, evaluating existing TDAs first before developing an evidence-based TDA. The operational handbook accompanying the 2022 guidelines includes two TDAs (one for those with and one for those without access to CXR) [32]. External validation of these TDAs is underway.

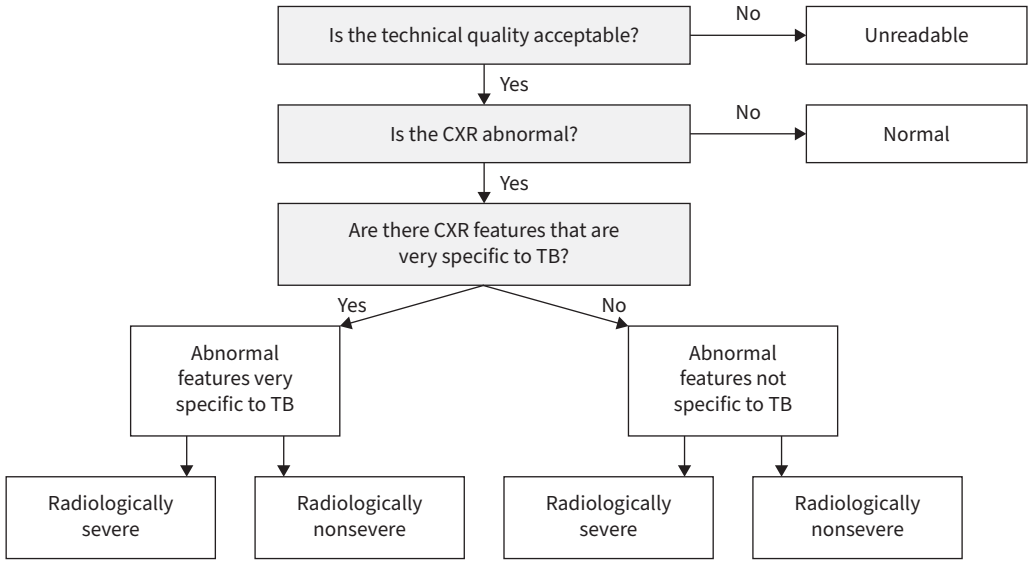

FIGURE 2 Algorithm for CXR interpretation in a child with presumptive PTB. When evaluating a CXR, the first step is to assess the quality of the images to determine whether they are readable. Poor-quality images can lead to over- or underdetection of pathology. Next, the reader must determine whether the CXR is normal or abnormal. A full understanding of paediatric CXR features requires training and practice. The thymus (a physiological feature, usually seen in children <5 years of age) and perihilar vascular markings are commonly misinterpreted as abnormal. CXRs with abnormal findings should be evaluated for the presence of TB-specific features. Additionally, CXR can be used to stratify treatment based on disease severity. Features of nonsevere disease are intrathoracic lymph-node TB without airway obstruction, uncomplicated TB pleural effusion (without empyema or pneumothorax), or paucibacillary, noncavitary disease confined to one lobe of the lungs and without miliary TB. Reproduced and modified from [29] with permission.

Microbiology

Prior to starting treatment for TB disease, best practice is to obtain at least one and preferably several samples for microbiological evaluation in an attempt to isolate *M. tuberculosis* (figure 4 and table 2). This serves to both confirm the diagnosis and provide a sample for DST (table 1).

Host biomarkers

A biomarker is a biological marker that can indicate a disease state, and several biomarkers have been identified to assist in the diagnosis of childhood TB [33, 34]. A seminal article published in 2014 demonstrated that a 51-gene signature could discriminate children with confirmed TB from children with other diseases with high sensitivity and specificity [35]. Ongoing proteomic and transcriptomic work is being carried out by several groups to identify a small number of proteins or genes that retain performance and could be translated into a point-of-care test. It is anticipated that point-of-care tests will be available in the next 5 years.

TPT

The WHO now recommends several TPT regimens of similar effectiveness and safety, regardless of HIV status (table 3) [27, 36, 37]. Choices depend on availability, guidelines, age and HIV status, preferences, contraindications and child-friendly formulations. For children living with HIV, the most critical component is the composition of the ART regimen.

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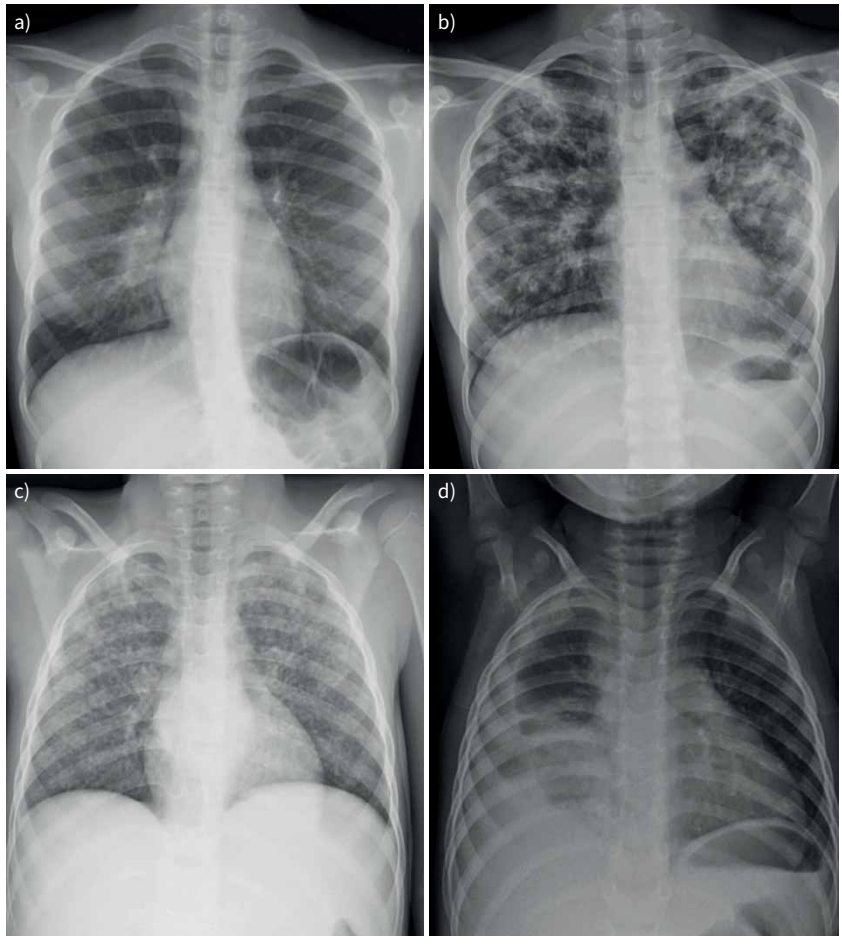

FIGURE 3 Examples of specific radiological manifestations of childhood TB. a) Uncomplicated lymph-node disease, b) adult-type disease with breakdown and cavities, c) miliary picture, and d) pleural effusion. Reproduced and modified from the Diagnostic CXR Atlas for Tuberculosis in Children – Image Library (https://atlaschild.theunion.org/) with permission.

For MDR-TB, the risk of infection and disease is likely to be similar to that for other TB contacts. Most international TB guidelines and networks recommend a fluoroquinolone-based preventive treatment on a case-by-case basis. Three clinical trials are currently underway that are likely to inform updated TPT guidance when results become available (ISRCTN identifier ISRCTN92634082, ClinicalTrials.gov identifier NCT03568383 and ANZCTR identifier ACTRN12616000215426).

Treatment of TB disease in children

The treatment principles for TB in children are the same as those for adults. The goal is to cure the patient with minimal side-effects, prevent relapse, reduce disease transmission and avoid the development of drug resistance. Anti-TB treatment is typically divided into an intensive phase with three or more drugs followed by a continuation phase with two or more drugs (table 4) [27]. Weight-band dosing and child-friendly formulations are available for

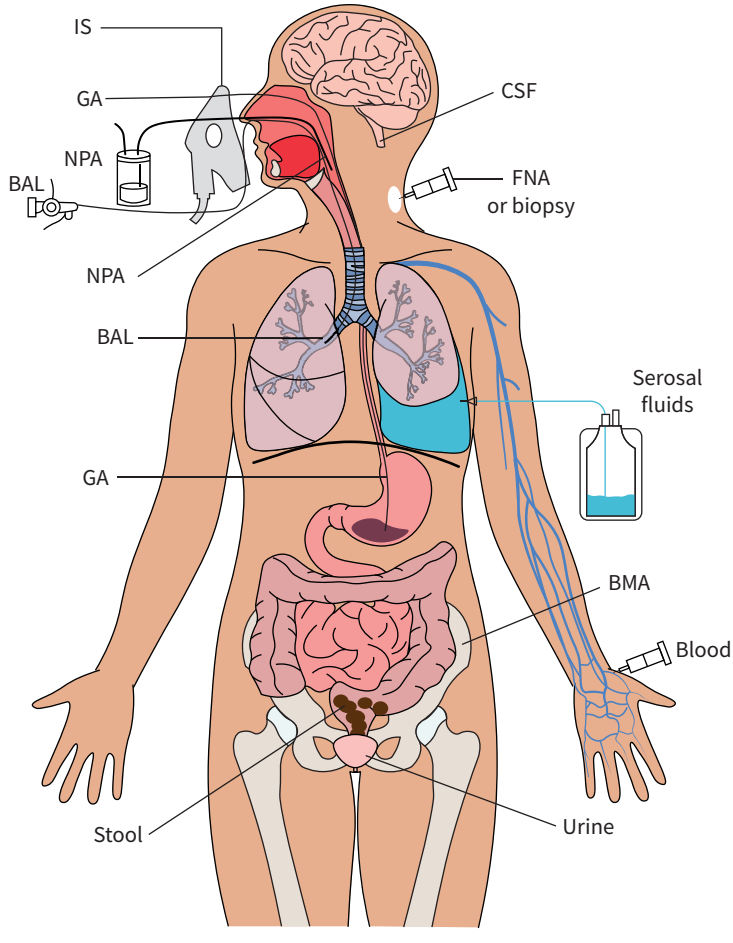

FIGURE 4 Respiratory and nonrespiratory samples for the diagnosis of TB in children. The choice of method depends on the site of disease; age; acceptability for the child, parents, health workers and other stakeholders; feasibility of collecting and preparing specimens in the local context; local availability of equipment, consumables and trained personnel; and tests. Respiratory samples for the diagnosis of PTB include: expectorated sputum (ES), induced sputum (IS), nasopharyngeal aspirate (NPA), gastric aspirate (GA), stool and bronchoalveolar lavage (BAL) (see table 2). Nonrespiratory samples include: 1) cerebrospinal fluid (CSF) obtained through lumbar puncture for diagnosis of TB meningitis through molecular tests, culture and biochemical analysis and cell counts of the liquid; 2) fine-needle aspiration (FNA) biopsy or excision biopsy for the diagnosis of TB lymphadenopathy with histology, molecular tests or culture; 3) serosal fluids and tissue (pleural, peritoneal, pericardial or synovial) obtained through a pleural, ascitic, pericardial or joint tap for diagnosis of pleural, abdominal, pericardial and bone/joint TB, respectively; 4) bone marrow aspirate (BMA) or blood, in severely ill people with suspected disseminated TB; and 5) urine – a clean catch or midstream urine sample for the diagnosis of genitourinary TB (Xpert MTB/RIF) or the detection of lipoarabinomannan antigen in children and adolescents living with HIV. The minimum recommended volumes/weights are 3 mL for ES, IS and BAL; 2 mL for NPA; 5 mL for GA and blood; 10 mL for gastric lavage (GL), CSF and urine; 5 g for stool; 1 mL for serosal fluids; and 1 mL for BMA. The optimal collection times are as follows: for GA, early morning before the child gets out of bed (to avoid emptying of the stomach after peristalsis begins); for ES, IS, GL, NPA and urine, ideally early morning; for the rest of the samples, any time. Age groups are: GA and NPA: <7 years; ES: >5 years; rest of samples: any age. Testing of samples should be carried out according to the WHO-recommended rapid diagnostic tests and specimen types in the 2022 guidelines: Xpert MTB/RIF for all samples; Xpert MTB/RIF Ultra for sputum, NPA, GA, stool, CSF and FNA; Truenat MTB and MTB Plus and loop-mediated isothermal amplification (TB-LAMP) for sputum; and lateral flow urine lipoarabinomannan for urine [27]. Conceptualisation by E. López-Varela; artwork by Alberto Rey (with permission).

https://doi.org/10.1183/2312508X.10025322

TABLE 2 Description of WHO-approved respiratory samples for the diagnosis of PTB

Specimen	Procedure	Advantages/disadvantages	Caregiver acceptability	Diagnostic accuracy: sensitivity/specificity (certainty of evidence)
Expectorated sputum	Expectoration of sputum without prior nebulisation	Advantages: low cost; noninvasive Disadvantages: not feasible in young children (<8 years)	High	Xpert MTB/RIF: 0.65/0.99 (moderate) Xpert MTB/RIF Ultra: 0.73 (low)/0.97 (high)
Induced sputum	Expectoration of sputum (either spontaneous or after nasopharyngeal aspirate) following hypertonic saline nebulisation	Advantages: noninvasive (if followed by expectorated sputum) Disadvantages: requires equipment, trained personnel, electricity and consumables; aerosolised transmission risk	Moderate	Xpert MTB/RIF: 0.65/0.99 (moderate) Xpert MTB/RIF Ultra: 0.73 (low)/0.97 (high)
Nasopharyngeal aspirate	Nasopharyngeal suctioning using a sterile catheter with a mucus trap/suctioning device while child in the supine position either directly or after induced sputum	Advantages: feasible in young children; less invasive than gastric aspirate Disadvantages: invasive; requires equipment, electricity, consumables, trained personnel and 2 h fasting; high level of discomfort; aerosolised transmission risk	Moderate	Xpert MTB/RIF: 0.46 (moderate)/ 1.0 (high) Xpert MTB/RIF Ultra: 0.46 (very low)/0.98 (low)
Gastric aspirate	Nasogastric aspiration of gastric juice (containing swallowed sputum) first thing in morning Gastric lavage: instillation of solution to "wash off" and recover sputum adhered to stomach wall if gastric aspirate <5 mL	Advantages: feasible in young children; common procedure for nurses Disadvantages: invasive; high level of discomfort; requires consumables, trained personnel and 4 h fasting	Low	Xpert MTB/RIF: 0.73 (very low)/0.98 (low) Xpert MTB/RIF Ultra: 0.64/0.95 (moderate)
Stool	Sampling from random stool, which can detect swallowed sputum from the respiratory system	Advantages: noninvasive Disadvantages: requires additional laboratory processing; must wait for bowel movement	High	Xpert MTB/RIF: 0.70 (low)/0.98 (high) Xpert MTB/RIF Ultra: 0.53/0.98 (moderate)

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TABLE 3 Currently available and recommended TPT regimens

Regimen[#]	Total duration, months	Notes
6H (daily)	6	More experience using it as TPT Poor adherence and completion rates Low cost Dispersible tablet available for children High risk of adverse events
3HR (daily)	3	Child-friendly formulation for <25 kg High adherence and completion rate Widely available in low-resource settings No child-friendly formulation for ⩾25 kg Not suitable for HIV-positive children due to DDIs with ART
3HP (weekly)	3	No dosage for <2 years No child-friendly formulation High-cost regimen High adherence and completion rate Low risk of adverse events Recommended regimen for adolescents with HIV on TDF/DTG/EFV/RAL-based ART
4R (daily)	4	No child-friendly formulation (liquid formulation not recommended but capsules can be opened and sprinkled onto or mixed with food/water for young children) High adherence and completion rate Low risk of adverse events DDIs with ART
1HP (daily)	1	High adherence and completion rate Not available for children <13 years of age Can be given to adolescents with HIV on TDF/DTG/EFV/RAL-based ART
MDR-TB regimens	6	Most guidance advises a 6-month regimen of daily therapy that includes a fluoroquinolone Three clinical trials currently underway to evaluate TPT for MDR-TB (see text)

H: isoniazid; R: rifampicin; P: rifapentine; DDI: drug–drug interaction; TDF: tenofovir disoproxil fumarate; DTG: dolutegravir; EFV: efavirenz; RAL: raltegravir. [#]: R- and P-containing regimens should be prescribed with caution in children and adolescents living with HIV and on ART because of potential DDIs. They can be used with EFV-based ART regimens.

https://doi.org/10.1183/2312508X.10025322

TABLE 4 Treatment options for drug-susceptible TB (DS-TB) and DR-TB in children and adolescents

Regimen	Drugs	Indications	Contraindications
DS-TB			
4-month	Intensive: 2HRZ or 2HRZE Continuation: 2HR	Age 3 months–16 years Nonsevere PTB or peripheral lymph-node TB	Infants <3 months or <3 kg Severe PTB or severe forms of EPTB Smear positive or positive for Xpert MTB/RIF or Xpert MTB/RIF Ultra with semi-quantitative grade medium or high
4-month	Intensive: 2HPMZ Continuation: 2HPM	Age >12 years PTB of any disease severity	Children <12 years Severe forms of EPTB
6-month	Intensive: 2HRZ or 2HRZE Continuation: 4HR	All ages (0–19 years) PTB or EPTB	Severe EPTB forms TBM, osteoarticular TB and disseminated (miliary) TB
6-month intensive	6HRZEto No continuation phase	All ages (0–19 years) Bacteriologically confirmed or clinically diagnosed DS-TBM	Children living with HIV
12-months	Intensive: 2HRZ or 2HRZE Continuation: 10HR	All ages (0–19 years) Severe EPTB (TBM, osteoarticular TB and disseminated/miliary TB)	
MDR-TB			
6-month BPaLM/BPaL	No M resistance: 6 months BPaLM With M resistance: 6–9 months BPaL	Aged ⩾14 years PTB or all forms of EPTB	TBM, osteoarticular TB and disseminated (miliary) TB Evidence of XDR-TB Evidence of resistance or allergy to any of the component drugs Pregnancy or breastfeeding Exposure to any of the drugs composing the regimen for ⩾30 days
Longer, tailored	Build a regimen using first group A drugs (B-Lzd-M/Lfx), group B (Cs-Cfz) and then group C (Dlm-Eto-PAS-Z-E)	All ages All forms of TB disease Duration dependent on severity of disease	

B: bedaquiline; Pa: pretomanid; L: linezolid; M: moxifloxacin; H; isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; P: rifapentine; TBM: tuberculous meningitis; Eto: ethionamide; Lzd: linezolid; Lfx: levofloxacin; Cs: cycloserine; Cfz: clofazimine; Dlm: delamanid; PAS: *p*-aminosalicylic acid. Notes: 1) addition of E in the intensive phase of HRZ-containing regimens for PTB and EPTB is recommended in settings with prevalence of HIV or H resistance. 2) For patients at risk of neuropathy due to H (PLHIV, malnutrition, infants, adolescents, high-dose H), pyridoxine (B_6) supplementation should be considered. 3) Adjuvant treatment is indicated for the treatment of TBM. 4) For the 6-month intensive treatment for TBM, higher dosages of R (22.5–30 mg·kg^{-1}), H (15–20 mg·kg^{-1}) and Z (35–45 mg·kg^{-1}) are used compared with the doses for PTB and other forms of disease. 5) Corticosteroids should be given at the time of initial diagnosis of TBM and are also indicated in the treatment of TB pericarditis. Corticosteroids are sometimes used in the management of other complicated forms of TB (*e.g.* complications of airway obstruction by TB lymph nodes), but the evidence base for other indications is poor. Prednisone is given orally (2 mg·kg^{-1} once daily, maximum dosage of 60 mg·day^{-1}) for 4 weeks. The dose should then be reduced gradually over 2–4 weeks before stopping.

first-line drugs (although not in all countries). Standard treatment for children is usually effective with better treatment success rates compared with adults [38]. Home-based treatment is always preferred, if possible.

Treatment of drug-susceptible TB

The WHO currently recommends two shorter 4-month regimens for children and adolescents with drug-susceptible TB (DS-TB) [27]. The first regimen was informed by the SHINE trial (Shorter treatment for minimal tuberculosis (TB) in children), which showed that for children with nonsevere TB using standard first-line drugs, a 4-month regimen was noninferior to a standard 6-month regimen. The 4-month regimen, using rifampicin, isoniazid and pyrazinamide, with or without ethambutol, is indicated for children aged 3 months to 16 years with nonsevere TB [27, 39]. The second regimen was informed by another trial in individuals aged ⩾12 years, which compared a rifapentine- and moxifloxacin-containing 4-month regimen with a standard 6-month regimen for both severe and nonsevere TB, finding that the shorter regimen was noninferior [39, 40]. Neither of these regimens can be used in those with EPTB, such as TBM, disseminated TB, osteoarticular TB or abdominal TB [27, 40].

Although TB treatment outcomes in children are excellent, optimal anti-TB drug dosing is required for certain subgroups at risk of subtherapeutic drug concentrations [41]. Suboptimal exposures have been observed in smaller children and in those weighing ⩾25 kg (who receive $mg \cdot kg^{-1}$ doses as for adults) when dosed according to the current WHO paediatric dosing recommendation using fixed-dose combination drugs [42]. Children living with HIV and those suffering from severe acute malnutrition may also experience suboptimal exposures [41–43].

Treatment of TBM

The evidence for TBM treatment is limited and is mostly extrapolated from PTB. Treatment outcomes for children with TBM are often poor, with high mortality and neurological disabilities, especially when disease is advanced [44–46]. The WHO recommends a 2-month regimen of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 10 months of rifampicin and isoniazid at standard doses [27]. Pharmacokinetic modelling suggests that higher rifampicin doses are required in children to achieve adequate rifampicin exposures [47], and in a paediatric TBM trial that recruited 37 children, neurocognitive outcomes in children receiving high-dose rifampicin ($30\ mg \cdot kg^{-1}$) were better than those who received the standard dose [48]. A pharmacokinetic and safety study of children with PTB (Opti-Rif trial: Pharmacokinetics and safety of high-dose rifampicin in children with TB) demonstrated that rifampicin dosages of up to 60–75 $mg \cdot kg^{-1}$ were needed to achieve target exposure and were safe. These higher dosages could contribute to improving TBM outcomes in children [49].

An alternative treatment regimen of 6 months using higher-dose rifampicin and isoniazid given with pyrazinamide and ethionamide has been conditionally recommended by the WHO, based on observational cohorts from South Africa [50]. Ethionamide is preferred as the fourth drug because of better cerebrospinal fluid penetration compared with ethambutol [51]. The SURE trial (Short intensive treatment for children with tuberculous meningitis), which is currently underway, will assess the efficacy of a modified shorter intensified 6-month regimen with optimised doses of rifampicin, isoniazid and pyrazinamide with levofloxacin in place of ethionamide (ISRCTN identifier ISRCTN40829906).

The neurological sequelae observed in TBM are attributed to the pathological impact of the host immune response and hypercoagulability [52]. Standard adjunctive therapy with corticosteroids for TBM reduces mortality risk in patients without HIV infection but does not prevent

 https://doi.org/10.1183/2312508X.10025322

long-term neurological impairment [46]. The antithrombotic, anti-inflammatory and anti-ischaemic effects of aspirin may reduce the risk of new infarcts and strokes [53]. The SURE trial will use a factorial design to secondarily randomise to aspirin *versus* placebo.

Treatment of MDR-TB

The treatment of MDR-TB has evolved rapidly with the introduction of new agents, use of repurposed drugs, and the transition from injectable agents to shorter and all-oral regimens.

The all-oral 6-month regimen containing bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) is the preferred option for adolescents >14 years with MDR-TB without (or with unknown) fluoroquinolone resistance. The BPaLM regimen was found to be noninferior to conventional treatment and was safe, with better treatment success of 89% *versus* 52% [54]. In the absence of paediatric safety or pharmacokinetic data, pretomanid is currently not approved for use in children <14 years. For younger children, regimens can be constructed by first using WHO group A drugs (linezolid, bedaquiline and a fluoroquinolone (levofloxacin or moxifloxacin)), group B drugs (clofazimine and cycloserine) and then any additional group C drugs to generate a regimen containing four to five effective drugs. Several groups suggest that children with severe disease can be treated for 9–12 months, while those with nonsevere disease can be treated for 6–9 months [55–57].

Bedaquiline and delamanid are now both recommended for use in children of all ages [27]. Safety data were similar to adult cohorts and model-derived dosages informed recommendations for use in children of all ages. Bedaquiline-containing regimens were associated with improved survival rates and favourable safety profiles in observational studies [58, 59]. Pharmacokinetic and safety data for delamanid show no safety concerns when given to children <3 years of age [25, 58].

For children and adolescents not on ART, HIV treatment should be initiated within 2 weeks of TB treatment initiation, except for TBM, where ART should be postponed for 4–8 weeks due to the high risk of immune reconstitution inflammatory syndrome.

Follow-up and monitoring

TPT

The WHO recommends that children and adolescents on TPT should have treatment follow-up monthly (if on a 3-month regimen) or every other month (if on a 6-month regimen). During follow-up visits, the child should be evaluated for adherence to treatment, TB symptoms and adverse events. Weight should be measured to adjust medication dosages if needed. It is important to record all children and adolescents initiating TPT. This is crucial for monitoring drug uptake (stock monitoring), adherence and outcomes of treatment. Electronic registers and databases are recommended by the WHO for collecting individual-level data to assess contacts of TB patients and PLHIV, and to monitor TPT initiation and completion [27, 36].

TB disease

Children should be assessed regularly for clinical progress, adherence, side-effects and dosage adjustments [25, 58]. Those with persistent symptoms should be assessed for other comorbidities, as well as exclusion of treatment failure. Children generally respond positively to DS-TB treatment with a very low risk (<5%) of serious adverse reactions [39, 60–63], while outcomes for children treated for MDR-TB are also very good [64].

Up to 10% of children treated for TB experience subclinical and transient elevations of transaminases, and routine liver function monitoring is not recommended except in cases where the

TABLE 5 List of anti-TB drugs

Name	Dosage, mg·kg^{-1} body weight	Adverse events per system	ART drug interactions
Isoniazid	7–15 (maximum dose 300 mg)	Dermatological: mild to severe maculopapular rash, pruritus, severe urticaria or anaphylaxis (rare) Systemic: moderate to severe hypersensitivity reactions and flu-like syndrome (rare) Haematological: mild to severe marrow suppression, which may result in decreased haemoglobin, platelets and white blood cells (rare)	
	High-dose isoniazid: 15–20 (maximum dose 400 mg)	Neurotoxicity: mild to severe peripheral neuropathy (common in severely malnourished and HIV-positive children, otherwise rare) Ophthalmic: severe optic neuropathy, neuritis (rare) Hepatic: mild to severe hepatitis, unexplained nausea, decreased appetite and vomiting may appear before jaundice (more common in HIV-positive children)	
Rifampicin	10–20 (maximum 600 mg)	Dermatological: mild to severe maculopapular rash, pruritus, severe urticaria or anaphylaxis (rare), mild transient flushing reactions (rare) Haematological: mild to severe marrow suppression, which may result in decreased haemoglobin, platelets and white blood cells (rare)	Rifampicin and nevirapine: rifampicin reduces plasma levels of nevirapine by ~40%, with little effect on efavirenz Rifampicin and lopinavir: rifampicin reduces plasma levels of lopinavir by ~80%
	TBM: 22.5–30 (maximum 600 mg)	Systemic: hepatitis, discoloration of secretions	Rifampicin and dolutegravir: rifampicin reduces plasma concentration of dolutegravir by 54% Rifampicin and ATV/r: there are significant interactions and they must never be co-administered

Continued

https://doi.org/10.1183/2312508X.10025322

TABLE 5 Continued

Name	Dosage, mg·kg^{-1} body weight	Adverse events per system	ART drug interactions
Pyrazinamide	30–40 (maximum 2000 mg) TBM: 35–45 (maximum 2000 mg)	Dermatological: mild to severe maculopapular rash, pruritus, severe urticaria or anaphylaxis (rare), mild transient flushing reactions (rare), mild to severe photosensitivity Systemic: hepatitis, elevated urate levels Musculoskeletal: arthritis/arthralgia	
Ethambutol	15–25 Drug-susceptible TBM: 17.5–22.5	Dermatological: mild to severe maculopapular rash, pruritus, severe urticaria or anaphylaxis (rare) Ophthalmic: severe optic neuropathy, neuritis (rare)	
Rifapentine	Dose per weight bands as outlined in WHO guidelines depending on whether used daily or once weekly	Systemic: hepatitis, discoloration of secretions, gastrointestinal disturbance	
Rifabutin	5–10	Uveitis, myelosuppression	
Levofloxacin	15–20	Sleep disturbance, gastrointestinal disturbance, arthralgia/arthritis, headache, idiopathic raised intracranial pressure	
Moxifloxacin	10–15 (maximum 400 mg)	Sleep disturbance, gastrointestinal disturbance, arthralgia/arthritis, headache, idiopathic raised intracranial pressure, QT interval prolongation	
Bedaquiline	Dose per weight bands as outlined in WHO guidelines	Headache, nausea, liver dysfunction, QT interval prolongation, arthralgia	Efavirenz: reduces the levels of bedaquiline so it is contraindicated to co-administer the two Protease inhibitors (LPV/r, ATV/r and darunavir): increase the plasma levels of bedaquiline, and can increase the risk of cardiac and hepatic toxicity; it is contraindicated to co-administer
Linezolid	15, once daily in children 1–15 kg 10–12, once daily in children >15 kg	Diarrhoea, headache, nausea, myelosuppression, peripheral neuritis, optic neuritis, lactic acidosis, pancreatitis	

Continued

TABLE 5 Continued

Name	Dosage, mg·kg^{-1} body weight	Adverse events per system	ART drug interactions
Clofazimine	2–5	Skin discoloration, ichthyosis, QT interval prolongation, abdominal pain	
Cycloserine or terizidone	15–20	Neurological and psychological adverse effects, severe depression and suicidal ideation in adolescents	
Delamanid	Dose per weight bands as outlined in WHO guidelines	Nausea and vomiting, dizziness, paraesthesia, anxiety, QTc prolongation, hallucinations and night terrors	Protease inhibitors (LPV/r, ATV/r and darunavir): increase the plasma levels of delamanid but with no clinical side-effect
Meropenem	20–40 every 8 h	Hypersensitivity reactions, seizures, nausea and vomiting, diarrhoea, hepatic and renal dysfunction; needs to be given intravenously	
Amikacin	15–20	Ototoxicity (irreversible) and nephrotoxicity, needs to be given *i.v.*; not recommended and should only be used in exceptional cases as salvage therapy	
Streptomycin	20–40	As for amikacin	
Ethionamide or prothionamide	15–20 (use in TBM)	Gastrointestinal intolerance, metallic taste, hypothyroidism	
***p*-Aminosalicylic acid**	200–300 in two divided doses	Gastrointestinal intolerance, hypothyroidism, hepatitis	
Amoxicillin-clavulanate (co-amoxiclav)	Only to be used with carbapenems	Gastrointestinal intolerance, hypersensitivity reactions, seizures, hepatic and renal dysfunction	
Pretomanid	No weight-based dosing proposed (used as part BPaL regimen)	Peripheral neuropathy, acne, anaemia, nausea and vomiting, headache, liver dysfunction, rash, pruritus, gastrointestinal intolerance	

TBM: TB meningitis; ATV/r: atazanavir+ritonavir; LPV/r: lopinavir+ritonavir; QTc: corrected QT interval; BPaL: bedaquiline, pretomanid and linezolid.

https://doi.org/10.1183/2312508X.10025322

TABLE 6 Research priorities

Epidemiology
Improve estimates of adolescent TB incidence and outcomes, including loss from treatment and mortality.
Estimate burden of nonsevere and severe PTB disease in children
Understand the burden, including incidence of disease and sequelae of distinct forms of EPTB, particularly CNS TB and other severe forms associated with poor outcomes
Determine burden estimates for the post-TB morbidity spectrum in children and adolescents to inform policy and planning
Determine age-disaggregated and risk group estimates for TB case notification and treatment outcomes in children at country level
Measure child and adolescent TB underreporting at country level through broader TB inventory studies
Characterise the co-occurrence of mental health disorders, including depression and anxiety, among older children and adolescents with TB
Prevention
Assess practical methods to optimise the full TPT cascade of care (identifying contacts, excluding TB disease, starting TPT and completing TPT)
Evaluate shorter TPT regimens, especially in the context of drug-resistant exposure and in children <2 years of age, including drug dosing and safety
Develop optimal point-of-care diagnostic tests for TBI among high-risk groups
Evaluate effectiveness, pharmacokinetic and safety data for TPT in the context of multimorbidity and MDR-TB among children
Estimate the duration of protection among at-risk subpopulations including within the context of high-TB-prevalence settings
Estimate the risk of drug resistance following TPT
Develop a more effective vaccine against TB disease for use in infants and all ages
Diagnosis
Develop better-performing TB screening tools and approaches with age-disaggregated and subpopulation performance data
Determine the regularity and outcomes of TB screening among at-risk subgroups
Develop more accurate tests to confirm TB disease from respiratory samples
Evaluate the role of mWRD in TB screening among children and adolescents and nonrespiratory samples.
In those with microbiologically confirmed disease, develop rapid drug-resistance tests that also include isoniazid
Validate the WHO treatment decision algorithms in diverse settings
Develop and validate computer-aided reading of digital CXRs for young children and improve the accuracy of this technology for older children and adolescents
Treatment
Conduct more timely dosing and safety studies of new drugs in children and adolescents before their licensing
Conduct treatment-shortening studies for DS-TB in children and include adolescents in adult TB treatment-shortening studies
Optimise treatment for TB meningitis, including adjuvant anti-inflammatory therapies
Optimise treatment of corticosteroid-refractory paradoxical inflammatory reactions in CNS TB
Design and evaluate artificial intelligence programmes for TB disease classification in children to facilitate uptake and rollout of the shorter TB treatment regimen
Conduct pharmacokinetic and safety studies on newer and repurposed TB drugs for DS-TB and MDR-TB among children including subpopulations
Operational research
Identify the causes of missed and delayed TB diagnoses in children and adolescents, and the best-practice interventions to promote earlier diagnosis of TB in children
Determine the most appropriate and most cost-effective TB service delivery models for children and adolescents
Develop and evaluate strategies to improve treatment adherence in adolescents
Evaluate programme integration strategies for paediatric TB, including those with HIV, maternal, neonatal and child health, adolescent health, nutrition and other relevant programmes
Evaluate the performance of the different WHO-recommended screening algorithms and tools for children in programmatic settings

Continued

TABLE 6 Continued

Better understand the barriers to diagnosis, treatment and treatment retention among children, adolescents and their families
Evaluate the preferences and needs of children, adolescents and their families with respect to TB diagnosis and treatment
Develop programmes to reduce stigma among children and adolescents and their families affected by TB
Evaluate the implementation of the new WHO-recommended TB treatment regimens for DS-TB (including TBM) and MDR-TB (standardised shorter and longer individualised treatment regimens) in programme settings
Evaluate the implementation of the shorter treatment options for TBI and the WHO-recommended algorithm for TB exclusion prior to TPT in programme settings

CNS: central nervous system; mWRD: molecular WHO-recommended rapid diagnostics; DS-TB: drug-susceptible TB; TBM: tuberculous meningitis. Data from [27, 76, 77].

patient has pre-existing hepatic disease, is experiencing symptoms of toxicity or is taking other hepatotoxic medications [61]. Follow-up CXRs are not routinely recommended except in cases of MDR-TB and in those with poor treatment response. For the child's treatment to be successful without interruption, the adult caregiver must be involved in the treatment plan. Adherence is one of the key determinants for successful treatment, and adolescents in particular experience substantial barriers to treatment adherence and are at risk for loss to follow-up from TB care. Adherence interventions (*e.g.* treatment support, digital technologies, adherence enablers) have been linked to better outcomes [65]. Despite limited data on their performance in children, remote adherence support techniques such as video-supported observed therapy have transformed adherence monitoring [65]. It is therefore important for TB programmes to implement mechanisms to follow up and monitor children on TB treatment. This includes assignment of outcomes upon treatment completion in line with WHO definitions. The latter have been revised into uniform outcomes that apply to both DS- and MDR-TB in the context of the newer treatment durations [66]. Counselling and health education of children, adolescents and caregivers, as well as nutritional screening, assessment and management, are integral components of TB treatment and care.

The management and follow-up of children with TB and other comorbidities (*e.g.* HIV) present additional challenges related to drug–drug interactions and toxicity overlap (table 5). The drug–drug interactions can be bidirectional (*e.g.* antiretroviral drugs may have an effect on anti-TB medicines and *vice versa*). HIV infection has been linked to subtherapeutic levels of the four first-line TB medicines resulting in lower peak concentrations and areas under the curve [67–69]. Rifampicin significantly lowers drug concentrations of antiretroviral drugs (including non-nucleoside reverse transcriptase inhibitors, protease inhibitors and integrase inhibitors) because it induces the cytochrome P450 system, P-glycoprotein and UDP glucuronosyltransferase [63, 70]. The recently conducted ODYSSEY trial (A randomised trial of dolutegravir-based antiretroviral therapy *versus* standard of care in children with HIV infection starting first-line or switching to second-line ART) confirmed that twice-daily dolutegravir in HIV-positive children receiving rifampicin is safe and counters the effects of rifampicin enzyme induction [63]. The optimal antiretroviral regimen for children includes dolutegravir-based regimens, so drug or dose adjustments to reduce potential drug–drug interactions should be considered [71]. It should be noted that drug interactions between antiretroviral medications and rifampicin occur both in the treatment of TB disease and when rifampicin is used as TPT.

Post-TB lung disease

Post-TB disease, including post-TB lung disease (PTLD), causes ill health, poor quality of life and death. PTLD refers to a range of pulmonary complications that occur after a TB episode

 https://doi.org/10.1183/2312508X.10025322

and has been linked to host–microbe interactions and immunological responses that may persist even after treatment completion [72, 73]. The complications, which vary in severity, include airflow obstruction, restrictive ventilatory defects and impaired gas exchange, and may present as persistent respiratory symptoms, abnormal lung function and/or abnormal CXRs. A consensus definition has been proposed for children as "evidence of chronic respiratory impairment in an individual previously adequately treated for PTB in whom active TB is excluded, and in whom no other cause of chronic lung disease is the predominant cause" [73]. The limited data on PTLD that do exist in children suggest substantial impairment [74]. For adults, up to two-thirds of individuals with a previous TB episode may present with lung complications, and a recently published systematic review documented a high burden of PTLD in low–middle-income countries with a pooled prevalence of 41.0% for persistent respiratory symptoms, 46.7% for abnormal lung function and 64.6% for radiological abnormalities [75]. Considering the prevalence of severe and complicated TB forms in children, coupled with diagnostic delays, it is likely that children with a previous TB episode have substantial post-TB lung damage. There is an urgent need for child-specific data on PTLD to inform future directions. The routine assessment of children with respiratory symptoms after successful TB treatment should also include a review of PTLD.

Research priorities

Several groups have identified critical priorities for research that will impact child and adolescent TB. We have integrated and adapted these priorities as documented in table 6.

Conclusion

Although child and adolescent TB remains a challenge, important progress has been made in diagnosis and treatment. Active contact tracing, screening and TPT can prevent disease spread. Early diagnosis is crucial and can be substantially improved, even with existing tools. Effective therapy is available, with optimised regimens being developed recently. Treatment outcomes are usually excellent in children, but access remains a challenge and addressing social determinants is necessary. By implementing evidence-based interventions and a comprehensive approach, we can reduce the burden of child and adolescent TB and improve outcomes for this vulnerable and neglected population.

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Support statement: ISGlobal receives support from: the Spanish Ministry of Science and Innovation through the Centro de Excelencia Severo Ochoa 2019–2023 Program (CEX2018–000806-S); and the Generalitat de Catalunya through the CERCA Program. E. López-Varela has received funding from the European Respiratory Society and the European Union's H2020 research and innovation programme under Marie Sklodowska-Curie grant agreement no. 847462. I. Munyangaju has received a fellowship from "La Caixa" Foundation (ID 100010434). The fellowship code is LCF/BQ/DI21/11860045.

Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10025322