MANAGEMENT OF TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

A Clinical Guideline
for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa

September 2024

health
Department:
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Foreword

The battle against tuberculosis (TB) remains one of the most significant challenges for our nation, particularly when it comes to our youngest and most vulnerable populations - children. Many advances have been made in managing TB in children and adolescents over the past decade, which have led to important progress and new knowledge, resulting in new global guidelines from the World Health Organisation (WHO) in May 2022. Persistent gaps in the diagnosis and treatment coverage of TB in children globally and South Africa, however, remain. The updated WHO guidelines, which include a significant amount of data on South African children and from South African researchers, provided the basis for the revised South African guidelines to improve the access to diagnosis and treatment of children and adolescents affected by TB in South Africa.

These revised South African guidelines reflect our ongoing national efforts to address the unique challenges posed by TB to children and adolescents in South Africa. The revised guidelines align with evidence-based WHO recommendations but consider the local and practical context of clinical care and health services in South Africa.

These new South African recommendations include the following key updates:

1. the use of additional specimens to confirm a diagnosis of TB in children;
2. the use of a clinical treatment decision algorithm to enable and support clinicians at the primary health care level to start TB treatment, and
3. practical guidance on implementation of treatment shortening for non-severe forms of TB in children and adolescents. Our goal is to enhance the quality of care provided to children with TB across the age spectrum, the TB disease spectrum, and with or without HIV. These guidelines and their implementation will further empower South African healthcare professionals to serve TB-affected children using the most current, practical, and effective tools available.

I extend my gratitude to the dedicated team of clinicians, researchers, and policymakers who serve on the National TB Think Tank Child, Adolescent and Maternal TB working group and have contributed to developing and revising these guidelines. Their expertise and unwavering commitment to improving child health in South Africa and globally have been instrumental in shaping these comprehensive new recommendations. Developing these guidelines was a collaborative effort between the Working Group and South African National and Provincial Department of Health representatives, with inter-departmental and cross-sectoral involvement. The National Essential Medicines List Committee (NEMLC) and the National Advisory Group on Immunization (NAGI) are also thanked for reviewing the evidence used in these guidelines.

As you delve into these revised guidelines, we encourage all stakeholders—from healthcare providers on the ground to public health officials, educators and community leaders—to engage with and implement these recommendations actively. Together, we can strengthen our response to TB in South Africa, reduce the burden of disease, and ensure that every child and adolescent in South Africa has the opportunity to grow up healthy and free from the shadow of tuberculosis.

Let us move forward with renewed vigour and a shared dedication to combating TB in South Africa. Our ultimate aim is to safeguard the health and well-being of our future generation.

Dr SSS Buthelezi
Director-General: Health
Date: 6 September 2024

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1 Introduction

The World Health Organization (WHO) estimated that approximately 1.25 million children aged 0-14 years developed tuberculosis (TB) globally in 2022.[1] Of these, only 612,800 children were notified and reported by TB programmes to WHO as diagnosed and treated, leaving half (51%) undiagnosed, untreated and/or not reported. The TB treatment coverage gap is the highest in young children, with 58% of children 0-4 years with TB being missed.[2] Improved diagnosis of TB in children and more child-friendly regimens are critically important to improve detection and close the treatment gap for children.

In 2022, South Africa reported 16,534 child (<15 years of age) TB notifications to the WHO.[1] This accounts for only 61% of the estimated 27,000 children with TB in the country, resulting in a treatment coverage gap of 39%. South Africa's progress towards achieving the targets agreed upon at the United Nations High-Level Meeting (UNHLM) for paediatric TB notifications and TB preventive treatment (TPT) initiation for child contacts <5 years has been set back by the negative effect of COVID-19 in 2020 and 2021.[3] Paediatric TB notifications increased from 66% in 2021 to 93% of the UNHLM target of 17,700 children in 2022. Yet, only 32% of the target for providing TPT for 52,350 child contacts younger than five was achieved.

To reach the ambitious targets set for 2024-2027 and find more children with TB, we need to increase TB disease detection among children and adolescents and provide them with high-quality TB care, including appropriate treatment, considering the extent and severity of the disease. In 2022, the WHO published revised paediatric TB guidelines and an accompanying operational handbook, which included several new evidence-based recommendations for diagnosing and treating TB in children and adolescents.[4] [5]

South Africa published its first national paediatric TB guideline in 2013: *'Guidelines for the management of tuberculosis in children'*.[6] This document replaces the 2013 guideline with updated recommendations on diagnosing, treating, and managing TB in children and adolescents, including recommendations on treatment shortening for non-severe TB.[7] This new guidance is aligned with the updated WHO guidelines but has been adapted specifically for the South African context.

1 Global tuberculosis report 2023. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

2 Roadmap towards ending TB in children and adolescents, third edition. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

3 United Nations High-level meeting on TB: TB Country targets. Available at https://www.stoptb.org/advocacy-and-communications/unhlm-tb-key-targets-and-commitments [accessed 21 November 2022].

4 WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

5 WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

6 Department of Health: South Africa. Guidelines for the management of tuberculosis in children 2013. DOH, Pretoria, South Africa, 2013.

7 Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, Hissar S, Choo L, Musoke P, Mulenga V, Mave V, Joseph B, LeBeau K, Thomason MJ, Mboizi RB, Kapasa M, van der Zalm MM, Raichur P, Bhavani PK, McIlleron H, Demers AM, Aarnoutse R, Love-Koh J, Seddon JA, Welch SB, Graham SM, Hesseling AC, Gibb DM, Crook AM, Team ST. Shorter treatment for non-severe tuberculosis in African and Indian children. N Engl J Med. 2022;386(10):911-22. doi: 10.1056/NEJMoa2104535. PubMed PMID: 35263517; PMCID: PMC7612496.

2 Epidemiology of TB in children

- TB in children and adolescents is common in high TB incidence countries like South Africa.
- Pulmonary TB (PTB) is the most common form of TB in children.
- Children typically have paucibacillary disease (have fewer bacilli), making it more difficult to confirm the diagnosis bacteriologically.
- Extra-pulmonary TB (EPTB) is also common and may coexist with PTB; presentation of EPTB varies with age.
- Children usually develop TB within 12 months following exposure to a source patient.
- Being of a younger age, living with HIV or HIV exposure, and/or having severe malnutrition are all risk factors for developing TB disease after TB exposure/infection.
- TB disease can be more severe and of rapid onset in infants and young children (<5 years of age).
- The BCG vaccine is not fully protective against TB disease but is especially protective against severe forms of TB in infants and young children and is, therefore, very important to give to all children at birth.
- The presentation of and approach to diagnosing PTB in adolescents (10–19 years) is similar to that for adults.
- Bacteriological confirmation is more likely in adolescents, who often have adult-type (cavitary) PTB disease.

Table 1 Important differences between children and adults

Important differences between children and adults	
Clinical picture	• Different pathophysiology means a different clinical picture. • Symptoms may be vague and may have a broad differential diagnosis. • As a result, TB in children could easily be missed or misdiagnosed.
Investigations	• Younger children tend to have few detectable bacilli in their sputum/other respiratory specimens (paucibacillary disease), which makes detecting and confirming TB bacteriologically more difficult. • Specimen collection is more difficult and more technical, e.g. gastric aspirates. • Different pathology produces a different radiological picture on chest x-rays.
Outcomes	• Children have very good outcomes if started on appropriate treatment timeously, but the highest risk of poor outcomes if not treated.

3 Pathophysiology of TB in children

Children usually develop TB after inhaling droplet nuclei containing *Mycobacterium tuberculosis (M. tb*), which have been coughed or breathed out by another person with infectious TB disease. This person is usually an adult or older child and can be called "the source patient". Droplet nuclei can remain in the air for several hours. When a child inhales these infected droplets, the *M. tb*, or TB bacilli, may breach the innate immune system to reach the terminal alveoli, where they multiply to form a parenchymal focus in the lung. This is called the primary focus or Ghon focus. The bacilli are then carried via the lymphatic system to the nearest mediastinal lymph node, which, together with the Ghon focus, form the Ghon complex (See Figure 1 below). The child may be asymptomatic or minimally symptomatic, and the infection is usually contained by the immune system (with low numbers of TB bacilli persisting) or completely cleared. Children with no symptoms and no radiological changes on CXR are classified as having TB infection (previously termed 'latent' TB) and do not have TB disease. These children should be considered for TB preventive treatment (TPT). However, if the bacilli overcome the constraints of the immune system and multiply, there is progression to symptomatic TB disease, which is accompanied by radiological changes on CXR (which may involve other sites of disease). EPTB usually develops after spreading via the lymphatic system or haematogenous spread in organs/systems other than the lungs and may be present without PTB changes in the CXR.

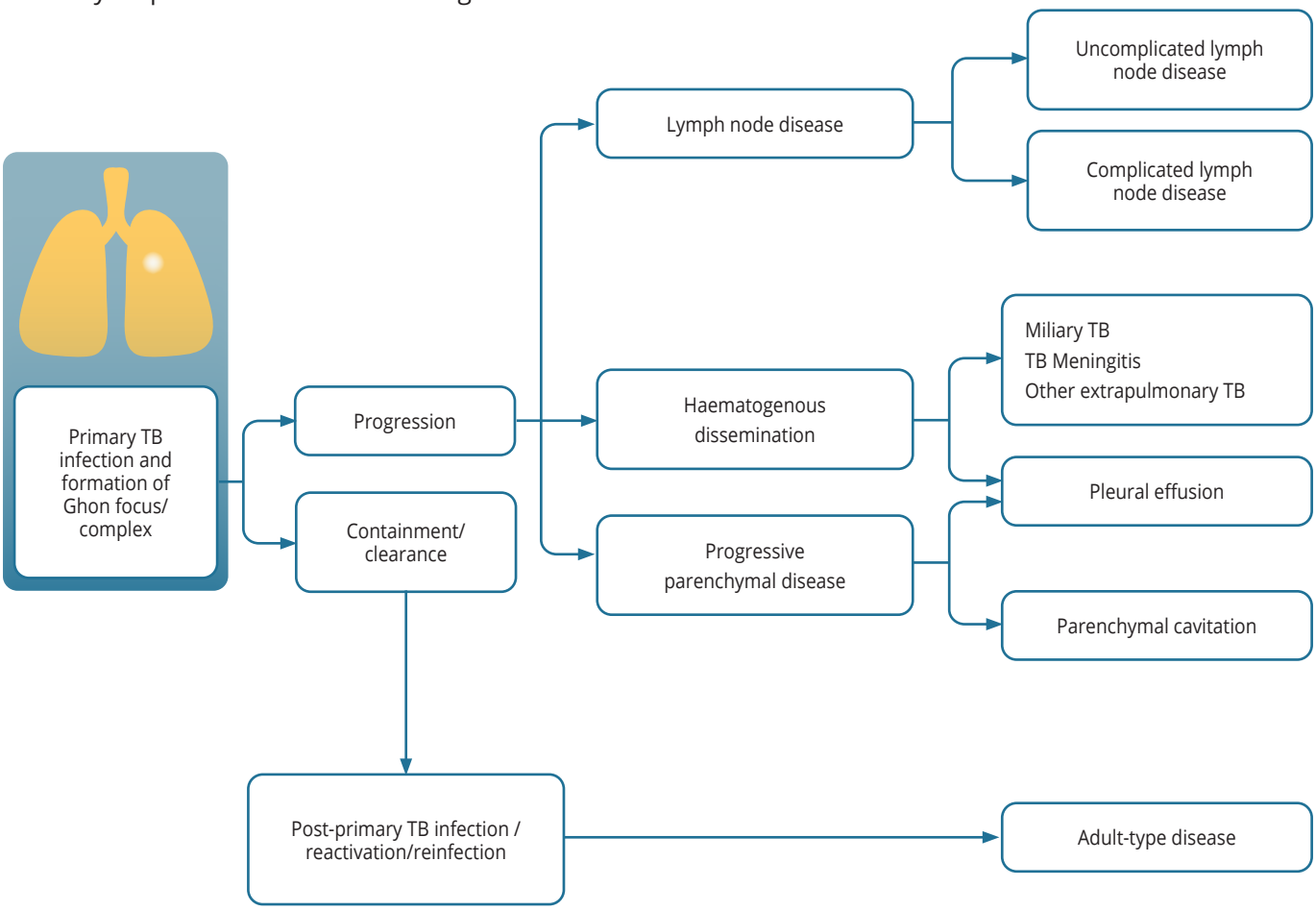


Figure 1 Pathophysiology of TB Disease [8]

8 Adapted form Palmer M, Seddon JA, Goussard P, Schaaf HS. Diagnostic CXR Atlas for Tuberculosis in Children. 2022

4 Important definitions in child and adolescent TB

Significant TB Exposure

A history of significant exposure to a TB source patient is defined as: "Exposure, within the 12 months before the child/adolescent presents with presumed TB, to a person (adult or adolescent) with pulmonary TB, within the same enclosed space for ≥ 1 night (e.g. at home or similar) or for frequent or extended daytime periods (e.g. at a school, crèche or similar), during the three months before the source/index patient started TB treatment."

TB Infection

A state of persistent immune response to stimulation by *Mycobacterium tuberculosis (M.tb)* antigens with no evidence of clinical TB disease is referred to as "TB infection," distinct from "TB disease." Most infected people have no signs or symptoms of TB but are at risk for TB disease. The term "latent TB" has been replaced by the term "TB infection", as children are mostly recently infected.

TB Disease

Disease caused by *M.tb*. TB disease can either be bacteriologically confirmed or clinically diagnosed.

Presumptive TB

A child or adolescent is believed to have presumptive TB when TB is considered a *possible* cause of illness in those who present with symptoms or signs suggestive of TB.

Clinical diagnosis of TB

A diagnosis made on the grounds of history, clinical findings, radiological features, exposure history, growth trend, or a combination of the above, and where bacteriological tests were either not performed or the results were negative.

Bacteriologically confirmed TB

The diagnosis of TB disease can be confirmed bacteriologically using one of the following tests: genotypic testing, i.e. TB-NAAT, mycobacterial culture, and/or smear microscopy for acid-fast bacilli (AFB).

Pulmonary Tuberculosis

Pulmonary tuberculosis (PTB) refers to TB involving the lung tissue, airways or draining lymph nodes (indicated by mediastinal and/or hilar lymph node enlargement on CXR). PTB is either clinically diagnosed or bacteriologically confirmed.

Extrapulmonary TB

Any bacteriologically confirmed or clinically diagnosed patient with TB involving organs other than the lungs, airways and intrathoracic lymph nodes.

Drug-susceptible TB (DS-TB)

M.tb strains that are susceptible to the first-line agents rifampicin and isoniazid.

Drug-resistant TB (DR-TB)

M.tb strains that are resistant to first-line anti-TB drugs.

5 Overview of the TB diagnostic and management process

Figure 2 provides an overview of the TB diagnostic and management process. The same process of screening, assessing/evaluating for TB disease, making a diagnosis, and treating and managing the diagnosis applies to TB infection, DS-TB, and DR-TB.

- If the process of assessing for TB determines that no TB disease is present, manage as per the **2023 TPT guideline.**
- If the process of evaluating for TB determines that drug-susceptible TB disease is present, manage as per this 2024 guideline for the **Management of Tuberculosis in Children and Adolescents**
- If the process of evaluating for TB determines that drug-resistant TB disease is present, manage as per the **2023 RR-TB Clinical Reference Guide.**

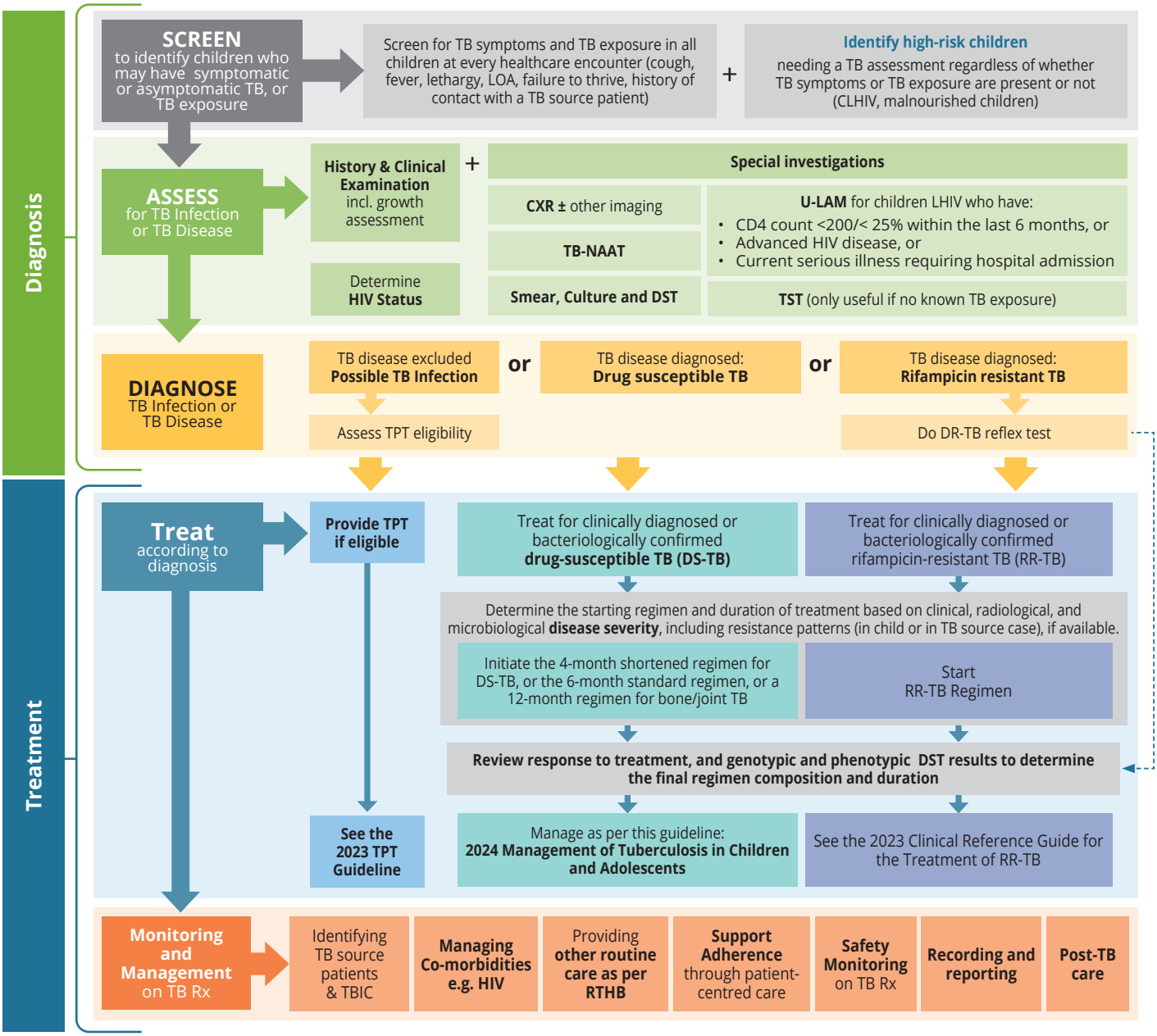


Figure 2 Overview of the TB diagnostic and management process

Abbreviations: CLHIV, children living with HIV; CXR, chest X-ray; DM, diabetes mellitus; DST, drug susceptibility test; DS-TB, drug-susceptible TB; DR, drug-resistant; LOA, loss of appetite; NAAT, nucleic acid amplification test; PCC, patient centred care; RR-TB, rifampicin-resistant TB; Rx, treatment; TB, tuberculosis; TPT, TB Preventive Therapy; TST, tuberculin skin test

6 The TB assessment in children and adolescents

TB should be considered part of the differential diagnosis in ANY ill child, especially if no alternative cause for symptoms is found or if there is a history of TB exposure.

Diagnosing TB in children and adolescents relies on an assessment of a combination of components or "puzzle pieces". These include:

- Patient history, including recent TB exposure and symptoms consistent with TB.
- Clinical examination, including growth assessment.
- HIV status (test if HIV status was negative at last test, or if HIV status is unknown).
- CXR (if available).
- Diagnostic testing (if available).
- Other investigations, as indicated by the site of extrapulmonary TB (EPTB), such as lumbar puncture, neuroimaging, ultrasound, fine-needle aspirates, and biopsies.

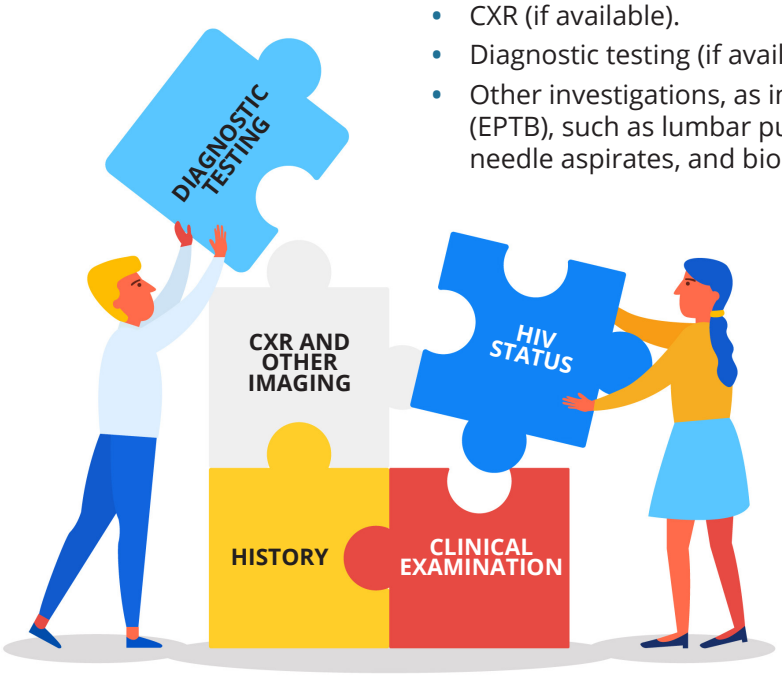


Figure 3 Pieces of the puzzle used to construct a TB diagnosis

Within the different puzzle pieces, the following aspects should be considered:

- Does the child or adolescent require immediate hospitalisation for inpatient care based on the severity of illness?
- Does the child or adolescent have typical TB-related symptoms, or could this be an atypical presentation of TB?
- What is the patient's weight, and how does it compare to previous weights?
- Has there been recent contact with a person with known TB or a person with TB-related symptoms who has not yet been diagnosed?
- Is the child or adolescent living with HIV?
- Does the child have risk factors for TB and for severe TB, such as being <2 years of age, living with HIV or severely malnourished?
- Is collecting and sending sample(s) for rapid diagnostic testing feasible?
- Is CXR readily available, and if it is done, are there abnormal features suggestive of TB?
- If diagnosis is uncertain, is it feasible and safe to review the child or adolescent in 1–2 weeks before making a treatment decision?

Note that the approach for adolescents is similar to that for adults. As for adults, bacteriological confirmation should always be sought; the clinical and CXR features of TB are more specific and readily identified in adolescents.

The specific details of **each puzzle piece** are described in the following text.

Interpreting the puzzle pieces together to **decide to treat TB** is illustrated in the **TB Treatment Decision Algorithm** in *Figure 6 on page 29*.

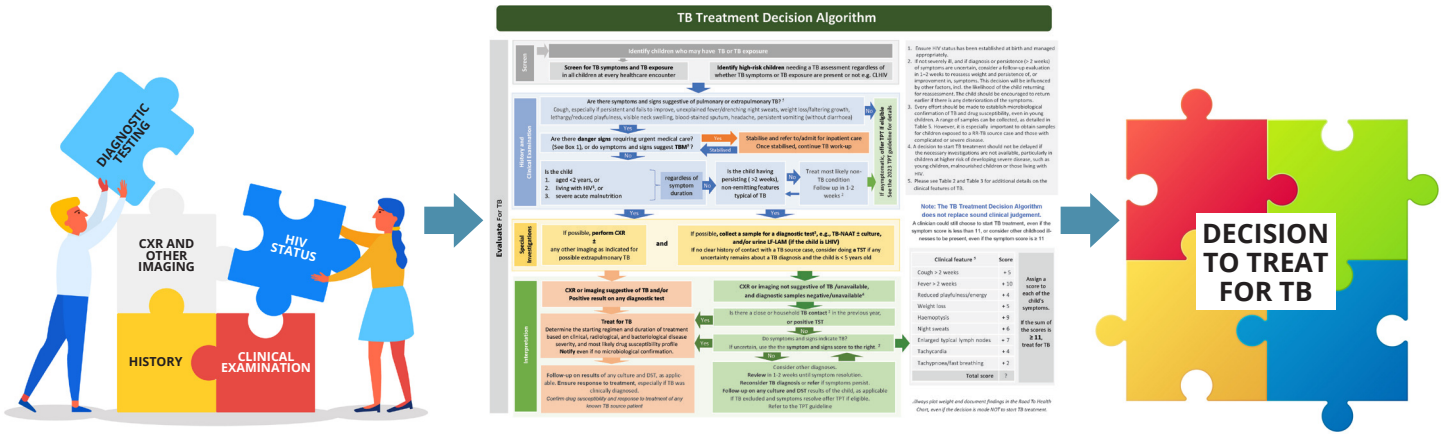


Figure 4 Building the TB "Diagnostic Puzzle"

In South Africa, there is a large burden of undiagnosed TB in children of all ages, especially children under five years of age. Difficulties around sample collection from younger children at the primary care level and a lack of confidence to diagnose TB and initiate treatment contribute to this TB treatment gap.

The TB Treatment Decision Algorithm in *Figure 6 on page 29* aims to facilitate TB diagnosis, particularly at the PHC level, where CXR and bacteriological testing may not be readily available.

A decision to start TB treatment should not be delayed if the necessary investigations are not available, particularly in children at higher risk of developing severe disease, such as young children, malnourished children or those living with HIV. If sufficient clinical or radiological evidence suggests TB, treatment may be started without bacteriological confirmation.

6.1 Triage assessment

Assessing a child should always start with a triage assessment and identification of any danger signs to determine if the child or adolescent requires immediate hospitalisation for inpatient care based on the severity of illness. Stabilise and refer to/admit for inpatient care as indicated.

Box 1 Danger signs needing urgent attention

General danger signs

- Unable to drink or breastfeed
- Vomiting everything
- Convulsions
- Unconscious or lethargic
- Any signs of shock

Signs of severe respiratory illness (any of the following)

- Chest indrawing
- Stridor in calm child
- Oxygen saturation < 92% on room air
- Central cyanosis

Signs of severe dehydration (2 of the following)

- Unconscious or lethargic
- Sunken eyes
- Unable to drink or drinking poorly
- Skin pinch goes back very slowly

Signs of meningitis (any of the following)

- Neck stiffness
- Bulging fontanelle
- Restless, continuously irritable

Signs of severe anaemia (any of the following)

- Severe palmar pallor
- HB < 7 g/dl

Adapted from the WHO Operational handbook on TB Module 5, SA national 2022 IMCI guidelines and Chapter 15: Respiratory System of the STG and EML for paediatric hospitals in SA, 2023

6.2 Patient history

Screen all children for TB exposure and symptoms at every encounter with the health system, whether in a health facility or at community level.

A history of TB exposure

A history of significant exposure to a TB source patient is defined as:

> *"Exposure, within the 12 months before the child/adolescent presents with presumed TB, to a person (adult or adolescent) with pulmonary TB within the same enclosed space for ≥ 1 night (e.g. at home or similar) or for frequent or extended daytime periods (e.g. at a school, crèche or similar) during the three months before the source/index patient started TB treatment."*

- Exposure may occur within a household, a crèche, a school, or within transport.
- The younger the child, the more likely it is to identify a close household contact with infectious TB.
- In older children and adolescents, contact with a source patient is often outside the household, such as at school or in the neighbourhood.
- Ask if the caregiver is aware of contact with a person known with TB or a person who is coughing.
- If a source patient is identified:
  - the drug susceptibility test result of the source patient should be reviewed.
  - the source patient's treatment regimen and response should be determined.
- If no definite source patient is identified, ask about contact with a person with a chronic cough. These potential TB source patients should be assessed for TB (reverse contact tracing).
- In many children with TB, there will be no identified TB source patient.

Symptoms typical of pulmonary TB

- Cough of any duration, but especially if it is persistent and fails to improve.
- Loss of appetite.
- Failure to thrive or weight loss.
- Fatigue, reduced playfulness, lower activity levels.
- Prolonged fever and/or drenching night sweats.

Most children and adolescents with TB develop unremitting symptoms that **persist for more than two weeks.** There should be a high index of suspicion, especially if symptoms persist (> two weeks) without improvement following other appropriate therapies (e.g., antibiotics for cough or nutritional rehabilitation for malnutrition).

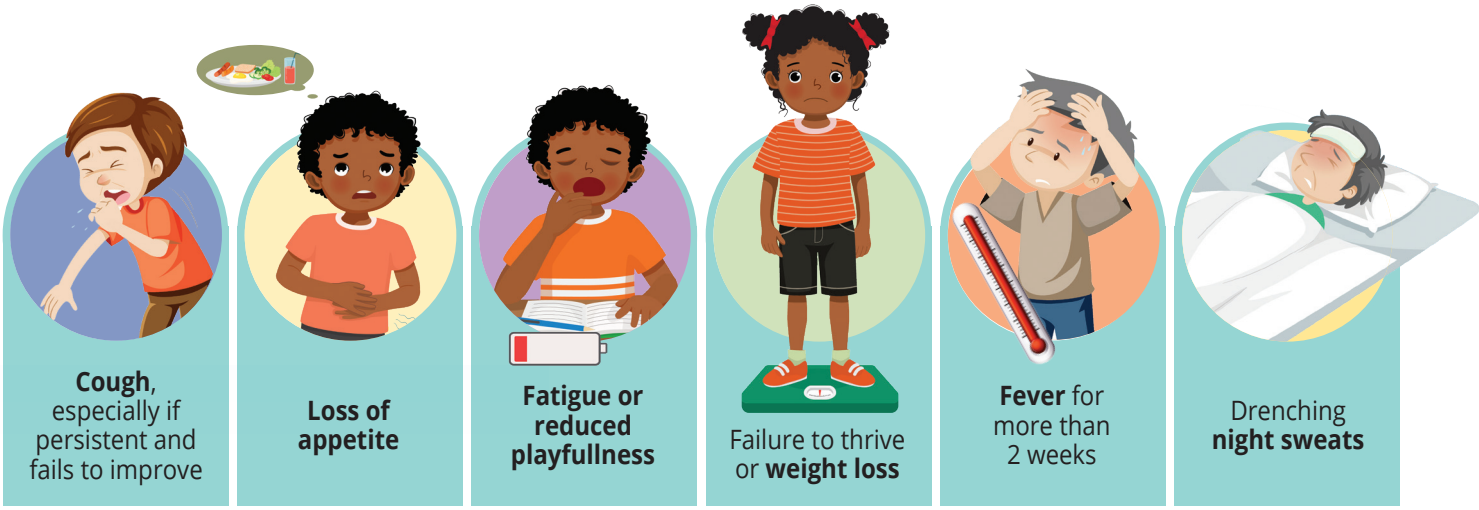


Table 2 and Table 3 provide additional details related to TB symptoms.

Table 2 Symptoms of PTB

Symptom	Comment
Cough	• Cough may be: o persistent and unremitting (> two weeks), especially if persisting despite treatment or o more acute and present as acute pneumonia, especially in infants and immunocompromised patients
Failure to Thrive	• Failure to gain weight or weight loss. • The caregiver may also note loss of appetite.
Reduced playfulness	• Persistent unexplained fatigue or decreased playfulness or activity reported by the parent or caregiver.
Persistent unexplained fever	• Persistent (> two weeks) and unexplained fever (> 38°C) reported by the caregiver or objectively recorded at least once. • Fever may be with, or often without, night sweats. • Night sweats, if present, are excessive and soak (drench) the bed or clothes. • Be clear to the caregiver that you are asking about an elevated body temperature. The caregiver can misinterpret 'fever' to mean 'flu-like symptoms'.
Noisy breathing	• May be as a result of airway compression by lymph nodes

Remember that:

TB symptoms may also be **atypical:**

- In high-risk groups, such as infants or children living with HIV (CLHIV) or severely malnourished children, PTB can present as **acute** pneumonia.
- Symptoms can be very vague, intermittent, varied and **non-specific.** Many children with TB have multiple healthcare visits before a diagnosis is made, and a high index of suspicion is therefore essential.

The following children need further investigation for TB regardless of whether TB symptoms or TB exposure are present or not:

- CLHIV (at HIV diagnosis, then yearly when viral load is checked).
- Children who completed TB treatment in the last two years: test for TB yearly for two years after completing TB treatment.

Symptoms of extrapulmonary TB

Symptoms of extrapulmonary TB will depend on the site of the disease, as detailed in *Table 3 on page 10.*

Table 3 Additional symptoms and signs related to extrapulmonary TB

Site of EPTB	TB symptoms
TB Meningitis (TBM) 	• The onset of TBM is often insidious, with symptoms usually present for days to weeks at diagnosis. • Early symptoms may be non-specific and sub-acute and include low-grade fever, cough, vomiting (mostly without diarrhoea), irritability, loss of weight/ failure to thrive and reduced playfulness. • Other symptoms include headache, seizures, unilateral weakness, behaviour changes, sleepiness, confusion or regression of milestones. • Younger children and CLHIV are particularly at risk of severe morbidity and mortality from TBM and can deteriorate fairly suddenly.
TB Lymphadenitis	New lumps (often in the cervical (neck) area) are typically asymmetrical, painless, present for more than two weeks, and do not respond to antibiotics. Lymph nodes are often visible and may or may not be associated with a discharging sinus.
Abdominal TB	Vomiting, abdominal distention, abdominal pain, diarrhoea, constipation, jaundice.
Pericarditis Pleural effusion	Shortness of breath, poor effort tolerance.
Bone/Joint/Spine	Refusal to weight bear or use limbs, swollen joints, regressed milestones, back or joint pain, gait abnormality, limping, new incontinence, visible deformities.
Skin	Chronic unexplained rashes; subcutaneous, often painful, nodules or skin discolouration changes or sinuses over lymph nodes or bone lesions.
Ear, Nose and Throat	Chronic, painless discharge from ear, 'lump' behind the ear.

The importance of follow-up assessments

If the child is not severely ill and there is uncertainty about diagnosis and persistence of symptoms, a follow-up evaluation in 1 to 2 weeks should be arranged to reassess weight and persistence of or improvement in symptoms. In low-risk children, especially those more than two years of age, not living with HIV, not severely malnourished, and not acutely ill, it is acceptable to treat the most likely non-TB condition and follow up the child in 1 to 2 weeks. This decision will be influenced by other factors, such as the likelihood of the child returning for reassessment (such as living proximity and availability of transport) and the availability of a community health worker (CHW) to facilitate retention in care if necessary. The parent/caregiver should be encouraged to return earlier if there is any deterioration of symptoms.

To assist future management decisions and document trends, always record clinical findings and plot weight in the Road to Health Book (RTHB), even if the decision is made NOT to start TB treatment.

6.3 Clinical examination

Vital signs

- Assess for increased temperature (> 38°C), increased respiratory rate (tachypnoea), and increased heart rate (tachycardia) for age:

Tachypnoea:

- children aged under 2 months: respiratory rate over 60/minute;
- children aged 2–12 months: respiratory rate over 50/minute;
- children aged 12 months to 5 years: respiratory rate over 40/minute;
- children aged over 5 years: respiratory rate over 30/minute.

Tachycardia:

- children aged under 2 months: heart rate over 160 beats/minute;
- children aged 2–12 months: heart rate over 150 beats/minute;
- children aged 12 months to 5 years: heart rate over 140 beats/minute;
- children over 5 years: heart rate over 120 beats/minute.

Failure to Thrive

The child should be weighed accurately, and the weight should be recorded in the weight-for-age curve in the child's RTHB. Weight should be **compared to previous weights in the past three months** as recorded in the RTHB.

Failure to thrive can be defined as any of the following:

- **Insufficient gain: clear deviation** from previous growth trajectory, i.e. the child is gaining weight, but not enough to remain on current growth curve.
- Growth faltering: documented **flattening of the growth curve** and **crossing of percentiles** in the preceding three months.
- Documented weight loss, i.e., the child weighs less than on previous visits
- Severe malnutrition (weight-for-age **Z-score ≤ −2)** in the absence of info on previous/recent growth trajectory.
- Any malnutrition, not responding to therapeutic nutritional treatment and deworming.
- Malnutrition in a CLHIV not responding to antiretroviral treatment (ART).

Always check contact history and weight, and record and compare them against previous weights in the road-to-health book.

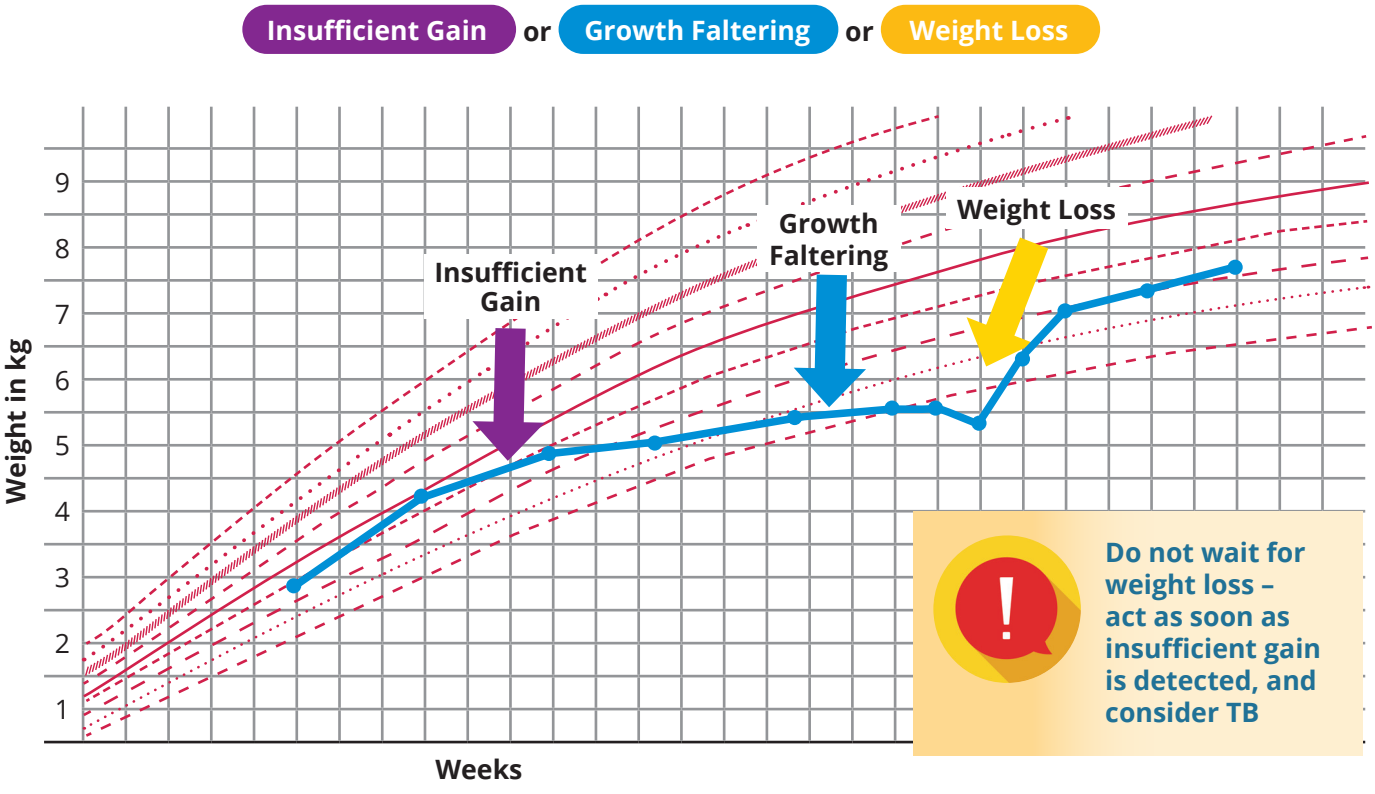


Figure 5 Failure to thrive illustrated on a growth chart

Respiratory system

- The child may have signs of **respiratory distress**, such as fast breathing, chest indrawing, head nodding, and grunting. These are danger signs: provide oxygen and manage as per the Integrated Management of Childhood Illness (IMCI) guidelines.
- Auscultation and percussion are usually normal but may reveal **lung disease,** e.g.,
    - Airway compression caused by enlarged tuberculous hilar lymph nodes may result in
        - asymmetrical and persistent wheeze not responsive to bronchodilator therapy and associated with other typical features of TB.
        - reduced air entry on one side of the chest with either hyperinflation or collapse.
    - Pleural effusion (reduced breath sounds and stony dull percussion).
    - Pneumonia/parenchymal changes (crackles, bronchial breathing).
    - Acute pneumonia not responding to an adequate course of antibiotics should increase the index of suspicion for TB.

Central nervous system

Look for clinical features of **TBM**:

- Neck stiffness is often absent during early disease in children, especially infants, but can be present.
- Assess power, tone, and reflexes, as well as cranial nerves and neurodevelopmental milestones, to look for focal neurological features that may be subtle at first.
- Ongoing vomiting without diarrhoea or preceding nausea should alert clinicians to the possibility of raised intracranial pressure.
- Features of raised intracranial pressure include a depressed level of consciousness, bradycardia, hypertension, asymmetrical pupils, an abnormal respiratory pattern, a bulging fontanelle, cranial nerve palsies, and papilledema, although the latter is rarely present.
- Children with TBM or tuberculomas often present to urgent care with altered levels of consciousness, focal neurological features and/or seizures.
- A history of exposure to an adult with infectious pulmonary TB and persistent symptoms are important in differentiating the symptoms of TBM from common childhood illnesses.
- Look for evidence of TB at other sites.
- Children with miliary TB should all be considered to have TBM regardless of the presence of symptoms or neurological signs.

TBM is a medical emergency and referral for inpatient care and investigations (lumbar puncture, imaging) are required. Initiation of treatment should not be delayed as early treatment will reduce the risk of death and/or permanent brain damage. Management of complications, such as seizures, is also important.

Lymphatic system

- **TB adenitis** may or may not be associated with other symptoms of TB.
- The **cervical lymph nodes** are the most common site of clinical presentation. The usual age of presentation is 2–10 years.
- Lymph node enlargement due to TB is typically:
  - Large (>2 x 2 cm), and visibly enlarged (not just palpable).
  - Painless, firm and asymmetrical - often multiple, discreet or matted.
  - Persistent (> 2 weeks) and not responsive to other treatments such as antibiotics.
  - Sinus and discharge may develop.

Other physical signs suggestive of extrapulmonary TB:

Table 4 The clinical presentation of extrapulmonary TB

Site of EPTB	Typical clinical presentation	Comment
TB Meningitis	• Headache, irritability/abnormal behaviour, vomiting without diarrhoea • lethargic/reduced level of consciousness • convulsions • neck stiffness • bulging fontanelle • cranial nerve palsies	• Usually young (<5 years) with disseminated disease and severely ill • Children with miliary tuberculosis should all be considered to have meningitis, even if no symptoms or neurological signs are present and even if CSF has a normal result
Miliary TB	• Non-specific symptoms, reduced activity/playfulness, persistent fever, loss of weight	
TB Adenitis	• Asymmetrical, painless, non-tender lymph node enlargement for > 2 weeks ± discharging sinus • Most commonly in the neck	• Most common form of EPTB in children • If axillary node enlargement on the same side as the BCG in an infant, consider BCG disease
Pleural TB	• Dullness on percussion and reduced breath sounds ± chest pain • No acute illness • If pus in pleural tap, consider empyema and refer	
Abdominal TB	• Abdominal distension with ascites or abdominal masses	
Pericardial TB	• Cardiac failure • Distant heart sounds • Apex beat difficult to palpate	
Spinal TB	• Chronic back pain in a child • May have lower limb weakness/paralysis/unable to walk • Bulge on the back of the spine	
TB of Bone and Joint	• Swelling end of long bones with limitation of movement • Unilateral effusion or chronic pain of usually the knee or hip, often following injury	

6.4 Investigations

- Every effort should be made to **establish bacteriological confirmation of pulmonary and extrapulmonary TB** and drug susceptibility, even in young children.
- Every effort should be made to obtain a **respiratory sample**, regardless of the presumed site of TB and **even if there is presumed extra-pulmonary TB, except if** bacteriological confirmation has already been established on a non-respiratory sample.
- Every effort should be made to train and equip healthcare workers at the primary care level to collect bacteriological samples.
- Bacteriological confirmation with testing for drug resistance should be conducted for all children and adolescents before treatment initiation. This is especially important for children and adolescents:
    - Who may have drug-resistant TB, such as when the known source patient has rifampicin-resistant/multidrug-resistant (RR/MDR)-TB or has had previous TB treatment.
    - Who are living with HIV.
    - Who have complicated or severe TB disease.
- Cerebrospinal fluid (CSF) provides lower yields of bacteriological confirmation compared to respiratory samples. A clinical diagnosis based on CSF chemistry and cell count, the clinical picture and neuroimaging is more likely. Clinicians should be vigilant in diagnosing TBM with early empiric treatment as soon as TBM is considered (see also *Box 2 on page 27*).
- As detailed in *Table 5 on page 17* and *Table 6 on page 18*, sputum and other samples can be collected to seek bacteriological confirmation of pulmonary and extrapulmonary TB.

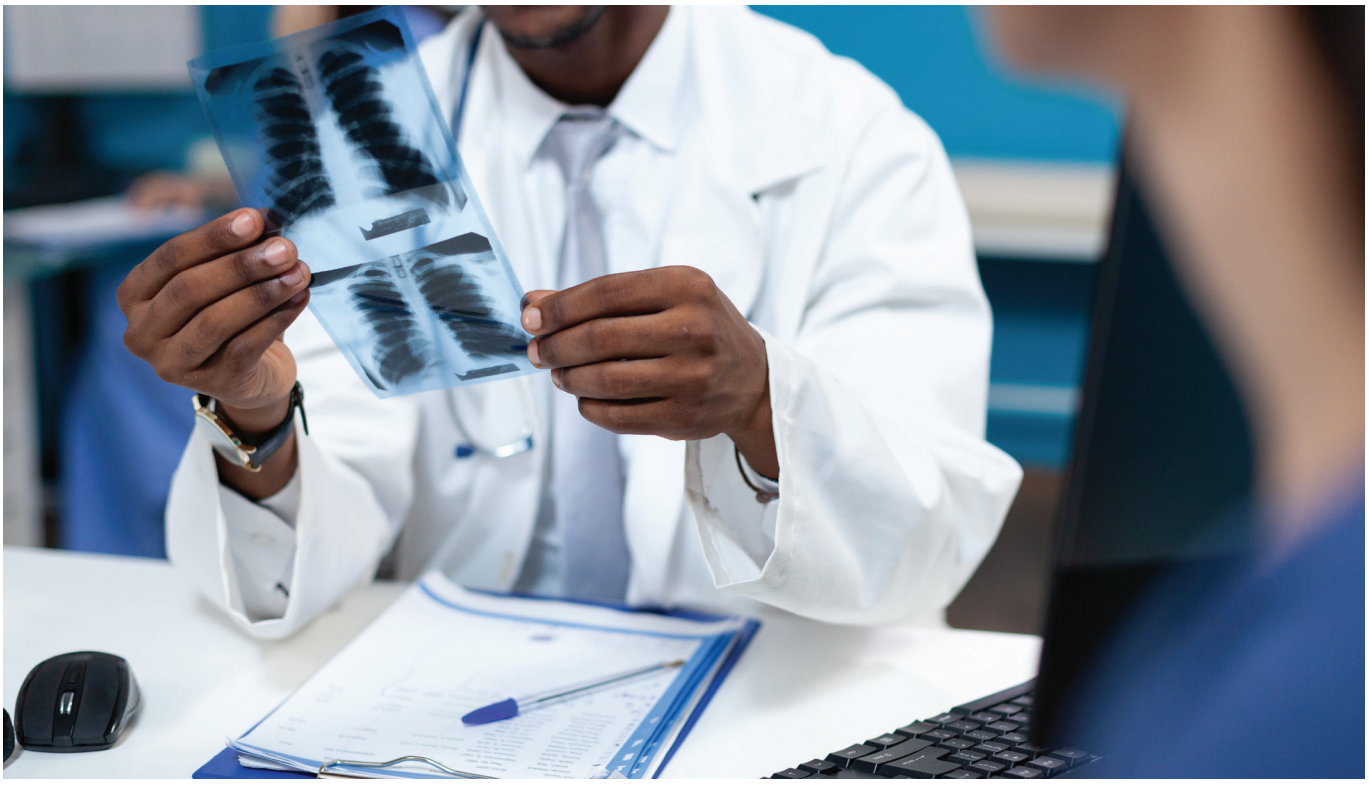
Despite challenges with confirmation of TB disease in young children, every effort should be made to establish bacteriological confirmation. However, if it is not possible to take samples to confirm TB, it is acceptable to diagnose, notify and treat based on history, clinical, and radiological findings (clinically diagnosed TB), as well as considering the drug susceptibility test results of the TB source patient.

See *Table 7 on page 26* for details on other special investigations, such as lumbar puncture, biochemistry, neuroimaging, and ultrasound, often used to diagnose TBM and other extrapulmonary forms of TB.

HIV testing

- HIV testing (accompanied by pre-and post-test counselling) should be offered to all children and adolescents being evaluated for presumptive TB or diagnosed with TB unless already known to be living with HIV.
- A positive HIV test raises the likelihood that persistent symptoms are attributable to TB.
- An early and accurate HIV diagnosis allows the child:
    - To be placed in the appropriate risk group to inform clinical decision-making (see ***Section 6.5 on page 28***).
    - To receive antiretroviral treatment (ART) and routine viral load monitoring and management to achieve viral suppression.
    - To receive comprehensive, integrated and family-centred care for TB/HIV coinfection (see ***Section 12 on page 58***).

The approach to diagnosis of TB in CLHIV is similar to that for HIV-negative children. However, health workers should have an increased degree of clinical suspicion of TB in CLHIV, as they are at a higher risk of developing TB disease, may have more rapid TB disease progression and are at higher risk of developing severe disease.



6.4.1 Tests available for TB diagnosis

Table 5 Overview of available tests to diagnose TB

	TB Investigation	Purpose	TAT	Possible outcomes
Tests for TB Infection	**Tuberculin Skin Test (TST)**	Confirmation of TB Infection when TB exposure status is unknown (and no previous positive TST or history of TB disease)	48-72 hours	Positive if ≥10 mm, or ≥5 mm in a CLHIV or malnourished child
Investigations to make the diagnosis of TB Disease	**Chest X-ray and other imaging**	To identify radiological changes in lungs & adjacent structures (or other organ systems is EPTB suspected) suggestive of TB disease and other non-TB-related abnormalities.	Variable	Lymph node disease with or without complications/ Miliary TB/ Parenchymal disease/ pleural or pericardial effusions
	TB Nucleic Acid Amplification Tests (TB-NAAT)	Bacteriological confirmation of TB. Identification of rifampicin resistance* If Rif-resistance is detected, DR-TB reflex testing should be done to detect resistance to isoniazid (INH) and second-line drugs	48 hours	MTB detected/ MTB not detected/ MTB trace/ Test unsuccessful Rif susceptible/ Rif resistant/ Rif unsuccessful/ INH resistant
	TB Culture	Bacteriological confirmation of TB, especially if initial NAAT negative Allows for DST (using TB-NAAT off the cultured isolate)	1-6 weeks	Positive for MTB complex or Negative for MTB complex
	Sputum Smear Microscopy	Not a routine or priority investigation in younger children who are seldom sputum smear positive for acid-fast bacilli (AFB) To monitor treatment response in older children and adolescents who were initially smear-positive on sputum Smear-positivity on sputum in a child suggests cavitary lung disease and severe TB disease	48 hours	AFB negative AFB positive: + ++ +++
	Urine-LAM	To facilitate the diagnosis of TB in symptomatic CLHIV who meet the eligibility criteria for testing	30 min	Negative/ positive (To be interpreted in the context of other clinical findings)
Investigations to determine drug susceptibility	**DR-Reflex Test**** To be done when TB-NAAT (on direct or cultured specimen) is positive for Rif-resistance	Xpert XDR cartridge (TB-NAAT that detects resistance to INH and some second-line TB drugs, including the fluoroquinolones. Also termed a genotypic DST)	48 hours	INH S / low-level R / R / unsuccessful FLQ S / low-level R / R / unsuccessful Amikacin S/R Ethionamide S/R
		Culture and Phenotypic DST to detect resistance to INH, BDQ, LZD, +/- CFZ, +/-DLM	6 – 9 weeks	INH S/R BDQ S/R LZD S/R +/- CFZ, +/-DLM
		A DR-Reflex test may include smear microscopy if there is sufficient sample volume.		
	Individualised Extended Phenotypic DST	Identifies susceptibility to multiple TB drugs used to construct a rescue regimen. Obtained by means of an email request to the laboratory when a RR-TB regimen fails, if resistance to BDQ or LZD has been detected, or if the patient has been previously exposed to second-line drugs.		

*Some assays (e.g., BDMax) can also detect INH resistance
**Testing is NOT always automatic. It is only automatic in the Western Cape because two samples are submitted upfront. It is also automatic if the RIF resistance is detected on a cultured sample. When doing direct testing on a TB-NAAT, all the sample is used up, and nothing remains for the DR-TB reflex testing. Therefore, a separate sample is required for reflex testing, which includes microscopy, Xpert XDR, culture and pDST.

Abbreviations: BDQ, bedaquiline; CLHIV, child living with HIV; DST, drug susceptibility testing; FLQ, fluoroquinolones; INH, isoniazid; LZD, linezolid; MTB, mycobacterium tuberculosis; NTM, non-tuberculous mycobacteria; Pa, pretomanid; R, resistance; rif, rifampicin; RR, rifampicin-resistant; S, sensitive; TAT, estimated turn-around time; TB, tuberculosis; U-LAM, urinary lipoarabinomannan assay

Table 6 The 'What', 'When' and 'How' for TB investigations in children and adolescents

TB Investigations: The 'What', 'When' and 'How'					
TB Investigation		**What does this test tell you?**	**What does this test NOT tell you?**	**When to do/not to do this test**	**Type of sample/other test details**
Facility-based tests	**Chest X-ray**	Typical radiological features can support a clinical diagnosis of TB. (see *Section 6.4.2 on CXR interpretation*)	A normal CXR does not exclude TB in a symptomatic child. Such results should be interpreted with the clinical history, symptoms and signs, TB-NAAT, U-LAM and TST (if no TB exposure). CXR abnormalities in children with PTB are often non-specific, meaning children with other common lower respiratory tract infections (or pneumonia) can have similar abnormalities.	For diagnostic purposes, do a CXR in any symptomatic child who is presumed to have TB, if available. In a TB-exposed child with no TB signs or symptoms, a CXR is not required to initiate TPT. It can be used to rule out TB, if available and if it can be interpreted on-site. The inability to do a CXR should not delay TPT initiation. Do a CXR at the time of any clinical deterioration on treatment	AP and lateral views are required in children to demonstrate mediastinal lymphadenopathy. PA views can be used in older children and adolescents.
	Urine LAM	A positive urine LAM provides clinical confirmation of TB disease in children living with HIV.	A negative U-LAM does not exclude TB A positive U-LAM does not provide any indication of drug susceptibility False-positive results are possible, especially if a bag specimen of urine is used.	Do a U-LAM test in the following children being investigated for TB: - For CLHIV and ALHIV admitted to hospital - For all symptomatic CLHIV seen in an outpatient setting with either: • CD4 count <25% (<5yrs) or <200 (≥5 yrs) within the last 6 months, or • advanced HIV disease, or • current serious illness warranting admission	Use urine sample for a lateral flow side room test A clean-catch urine sample or an in/out urine catheter sample will provide a more reliable test
	Tuberculin Skin Test (TST)	A positive TST confirms that a child has been infected with TB, now or in the past.	A negative TST does not exclude TB infection or TB disease. A positive TST result does not differentiate between TB infection and TB disease.	A TST provides no additional information on a child who is already known to have TB exposure. It has a role to play in an ill child with vague features that might be due to TB and in whom TB exposure is unknown. TST requires a functional immune system and sufficient time after TB exposure (typically > two weeks) to mount an appropriate response. There are multiple reasons for false negatives and false positives.	Done in the facility by a healthcare provider. It can only be read 48 hours after administration.

Abbreviations: ALHIV, adolescents living with HIV; AP, antero-posterior; CLHIV, child living with HIV; DR-TB; drug-resistant TB; DST, drug susceptibility testing; MTB, mycobacterium tuberculosis; NTM, non-tuberculous mycobacteria; PA, postero-anterior; rif, rifampicin; RR, rifampicin resistant; TB, tuberculosis; TPT, TB preventive therapy; U-LAM, urinary lipoarabinomannan assay

TB Investigations: The 'What', 'When' and 'How'

	TB Investigation	What does this test tell you?	What does this test NOT tell you?	When to do/not to do this test	Type of sample/ other test details
Laboratory-based tests	**TB Nucleic Acid Amplification Tests (TB-NAAT)**	Detects the presence of TB DNA and can detect resistance to rifampicin ± INH Provides bacteriological confirmation of TB.	**A negative NAAT test does not rule out TB, particularly in children with severe or extra-pulmonary disease. Therefore, a negative result should be viewed in the context of history and clinical and radiological findings, and treatment may be started if the overall picture suggests TB, even with negative NAAT results.** TB NAAT cannot differentiate between the DNA of live and dead bacilli and may remain positive for up to 2 years after successful treatment. It should, therefore, not be routinely used as a test to monitor treatment response.	Do a TB-NAAT for diagnostic purposes, to confirm TB and to detect rifampicin resistance in any symptomatic child who is being assessed for TB, if available. Always attempt to get a respiratory sample before treatment initiation, regardless of the presumed site of TB and even if there is presumed extra-pulmonary TB. However, barriers to sample collection should not become barriers to treatment. If sufficient clinical or radiological evidence suggests TB, treatment may be started without bacteriological confirmation. TB NAAT should be prioritised over TB culture in a sample with limited volume due to the speed of results.	Potential samples include sputum, induced sputum*, gastric aspirates, nasopharyngeal aspirates and stool. *Note: Stool samples cannot be cultured.* Tracheal aspirates and broncho-alveolar lavage may be possible in a hospital setting. Also, fine-needle aspirates, aspirates from pleural, pericardial, or joint effusions, and CSF. CSF (see Box 2) Aspirated pus/pus swabs from any abscess/ site where TB is presumed. Fluids from sinuses and ear canals can be tested but are unlikely to yield accurate NAAT results. Specimens may be obtained through spontaneous expectoration, sputum induction, gastric aspirates, nasopharyngeal aspirates, or any other fluid or tissue suitable for culture.
	Culture	The most sensitive indicator for bacteriological confirmation of TB and indicates viable, active bacilli, as well as the type of TB (MTB vs NTM). Culture-positive children might be smear-negative but are still infectious. Allows for drug susceptibility testing (DST).	Although a TB culture does not directly provide drug susceptibility results, genotypic and phenotypic drug susceptibility testing can be done on the cultured specimen if required. Typically, a treatment decision needs to be made before the culture result is available. TB treatment or TPT initiation should not be delayed while awaiting the culture results if there is sufficient clinical and/or radiological evidence to determine infection or disease. However, results should still be checked at each visit for confirmation and drug susceptibility, even after the treatment decision has been made.	Very helpful if the initial TB-NAAT was negative or inconclusive. If the initial TB-NAAT showed rifampicin resistance, genotypic and phenotypic DST should be performed as part of DR-TB reflex testing.	
	Smear microscopy	Provides bacteriological confirmation of mycobacterial infection, and if on sputum, is a marker of infectiousness. Smear-positivity on sputum in a child suggests cavitatory lung disease and is, therefore, an indication of severe TB disease.	A negative smear does not exclude TB. A positive smear does not indicate the type of TB or drug susceptibility. If negative at baseline in older children, don't repeat smear microscopy to monitor smear conversion (as done in adults) unless clinically deteriorating.	At primary diagnosis of TB, after a positive TB-NAAT result and before treatment initiation. Due to low sputum volume and yield, TB-NAAT should be prioritised, followed by culture and DST. Then, smear microscopy should only be performed if sufficient specimen remains. It is not a priority investigation in younger children who rarely have cavities.	

*Younger children, particularly those under six, often cannot expectorate adequately. In these patients, induced sputum (induction with nebulised salbutamol followed by nebulised hypertonic saline and nasopharyngeal aspiration) OR gastric aspirate OR nasopharyngeal aspiration (without induction) can be performed.

6.4.2 Chest X-rays

- CXR is an important tool for diagnosing PTB in children, many of whom are bacteriologically negative or unable to produce sputum.
- CXR is also important in determining the severity of pulmonary disease to make treatment decisions for shorter 4-month regimens in patients of non-severe TB.
- CXR is very useful in identifying forms of EPTB, such as miliary TB, pleural TB, and pericardial TB.
- The following TB-related abnormalities may be visible on CXR:
    - Enlarged hilar and/or paratracheal lymph nodes
    - Narrowing or compression of large airways
    - Opacification in lung tissue
    - Collapse of lung lobe
    - Miliary pattern in lung tissue
    - Cavitation (tends to occur more in older children)
    - Pleural effusion
    - Pericardial effusion
    - Abnormality of the thoracic vertebra or paravertebral abscess
- CXR abnormalities of PTB in children living with HIV are similar to those in HIV-negative children.
- TB-related abnormalities on CXR in a child with symptoms suggestive of TB are indicative of a TB diagnosis, even if bacteriological tests are negative or could not be done.

The CXR images on the following pages are extracted from resources provided by the International Union Against Tuberculosis and Lung Disease ("the TB Union"). These helpful resources can be accessed at the following links:

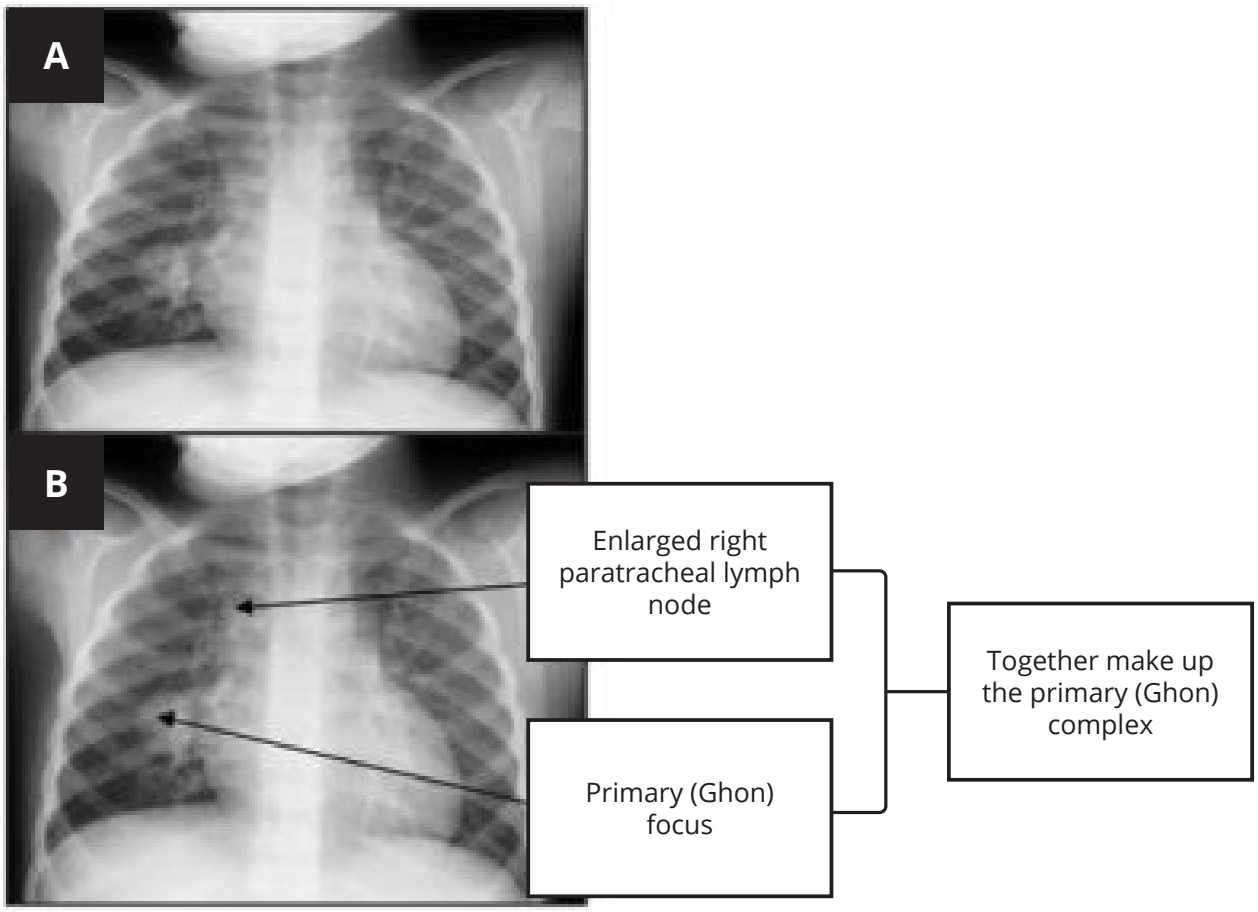
Child TB Desk Guide

https://theunion.org/sites/default/files/2023-06/Child%20TB%20Desk%20Guide%202023_Africa_0.pdf

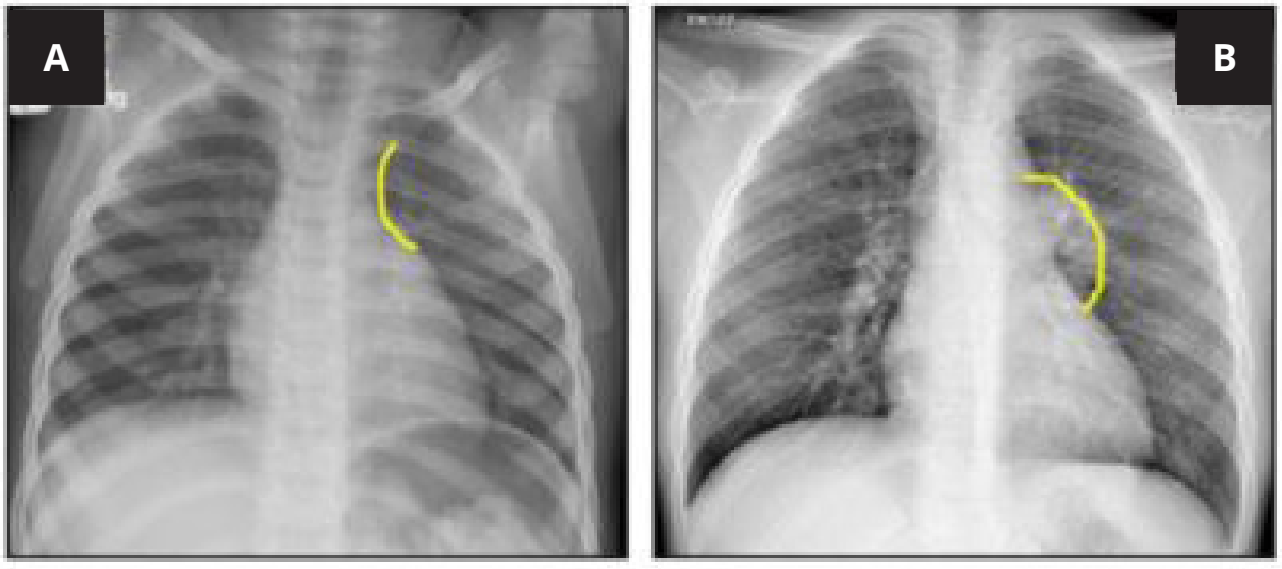
The Union Diagnostic CXR Atlas for Tuberculosis in Children

https://theunion.org/sites/default/files/2022-03/The%20Union_Diagnostic%20Atlas%20for%20TB%20in%20Children_2022.pdf

CXR abnormalities seen in children with PTB



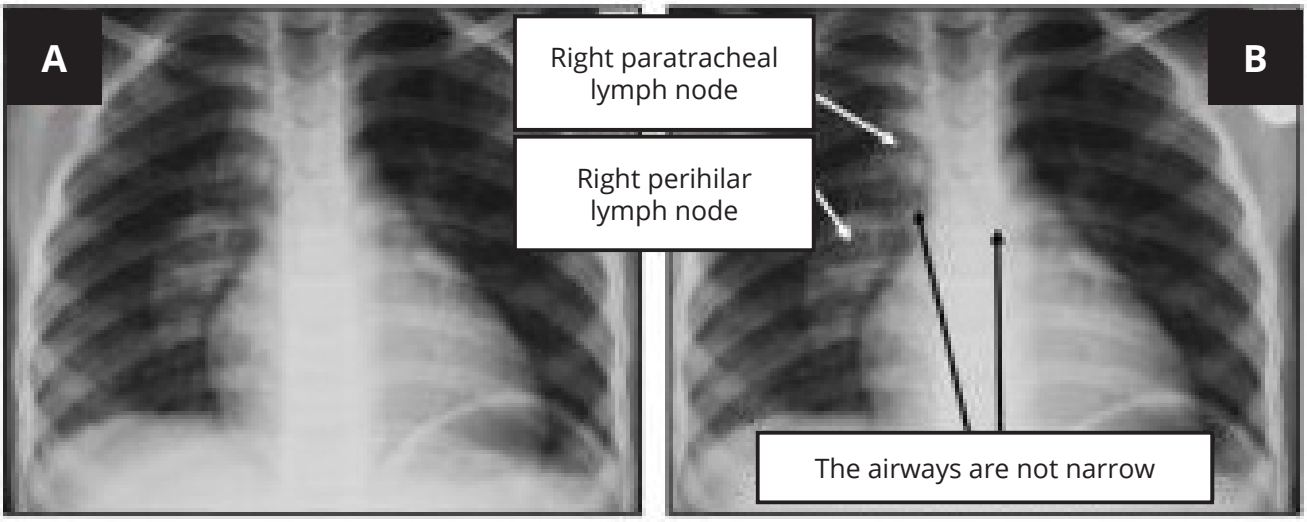
CXR (B) is an annotated version of CXR (A). This CXR shows a primary (Ghon) complex.



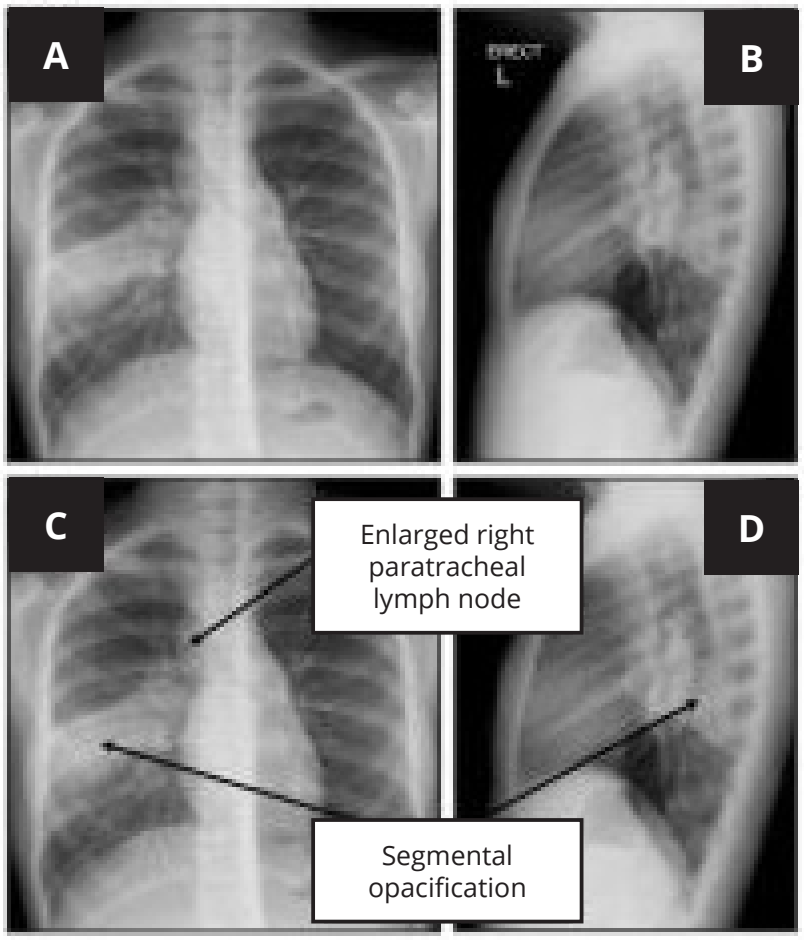
CXR (A) is normal; note that the hilar region has an inward convex shape.

CXR (B) is abnormal with loss of clear curve due to an enlarged left perihilar lymph node. This indicates radiologically **non-severe** disease.

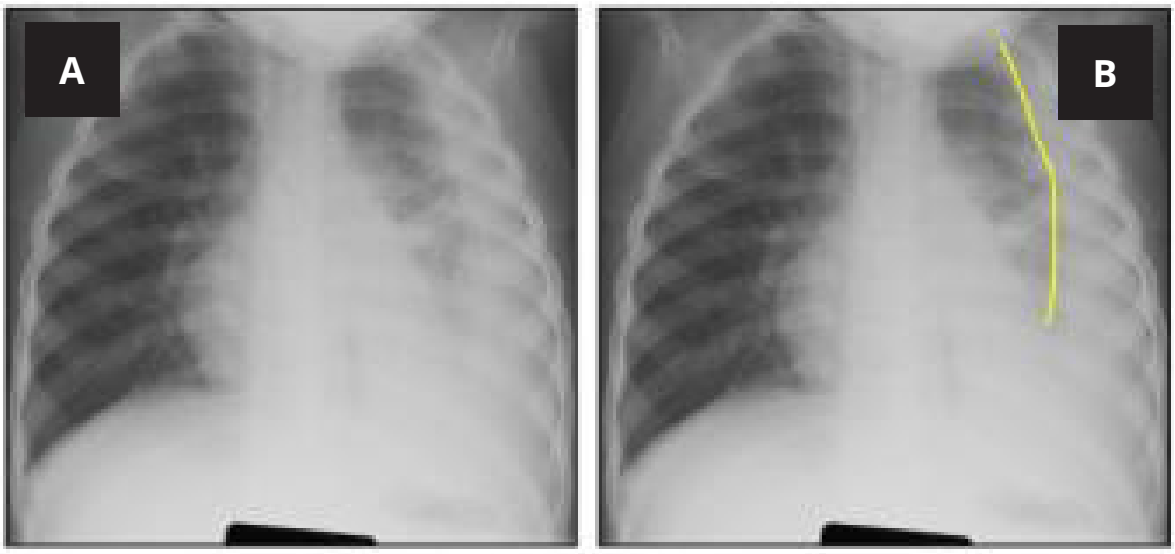
Source: International Union Against Tuberculosis and Lung Disease. Diagnostic CXR Atlas for Tuberculosis in Children: A Guide for Chest X-Ray Interpretation. Second Edition. Paris, France: The Union, 2022.



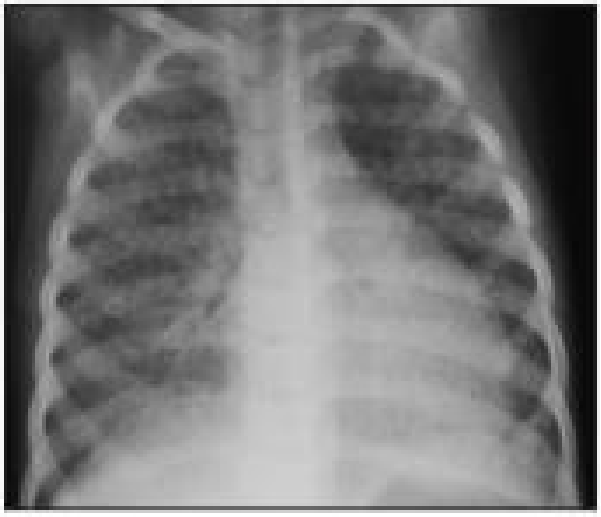
CXR (B) is an annotated version of CXR (A), which was taken from a 3-year-old child. This CXR shows enlarged paratracheal and perihilar lymph nodes on the right, with no airway or parenchymal involvement. This indicates radiologically **non-severe** disease. CXR (B) is abnormal with loss of clear curve due to an enlarged left perihilar lymph node. This indicates radiologically **non-severe** disease.



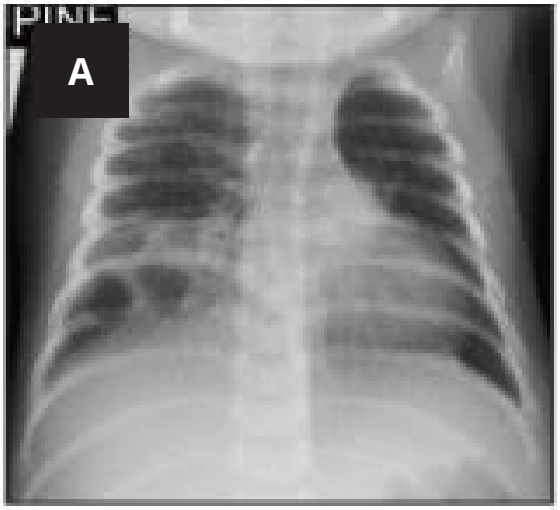
CXR (A) and (B) are a set of anterior to posterior (AP) and lateral CXRs taken from a 4-year old child. CXRs (C) ad (D) are annotated versions of the same set of CXRs. There is segmental opacification of the right lower lobe, with right-sided paratracheal lymph nodes. This indicates radiologically **non-severe** disease.



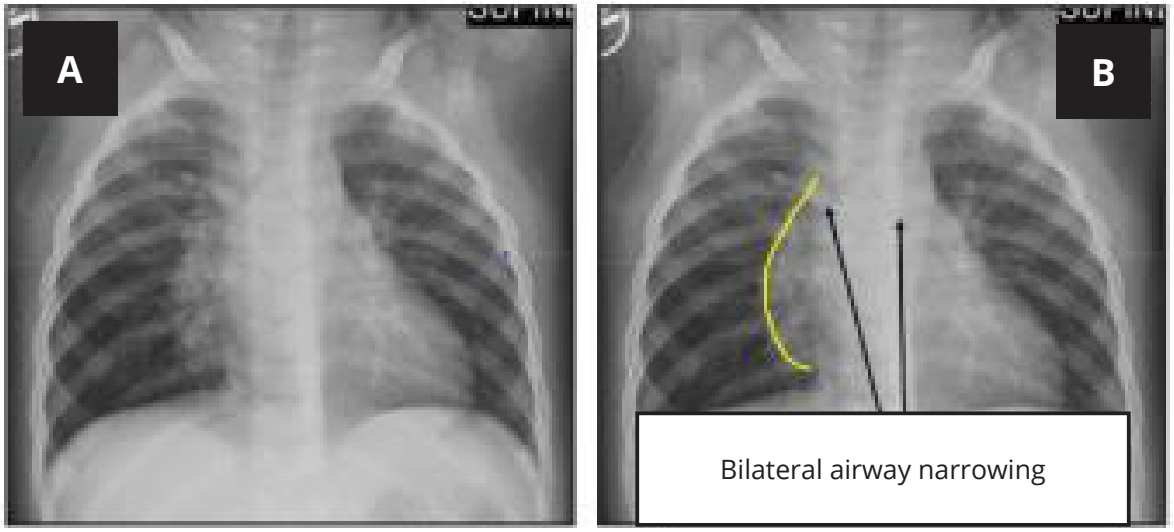
This CXR was taken from a 7-year-old child showing a left-sided pleural effusion. In addition, there is the appearance of underlying lung parenchymal disease. This indicates radiologically **severe** disease.



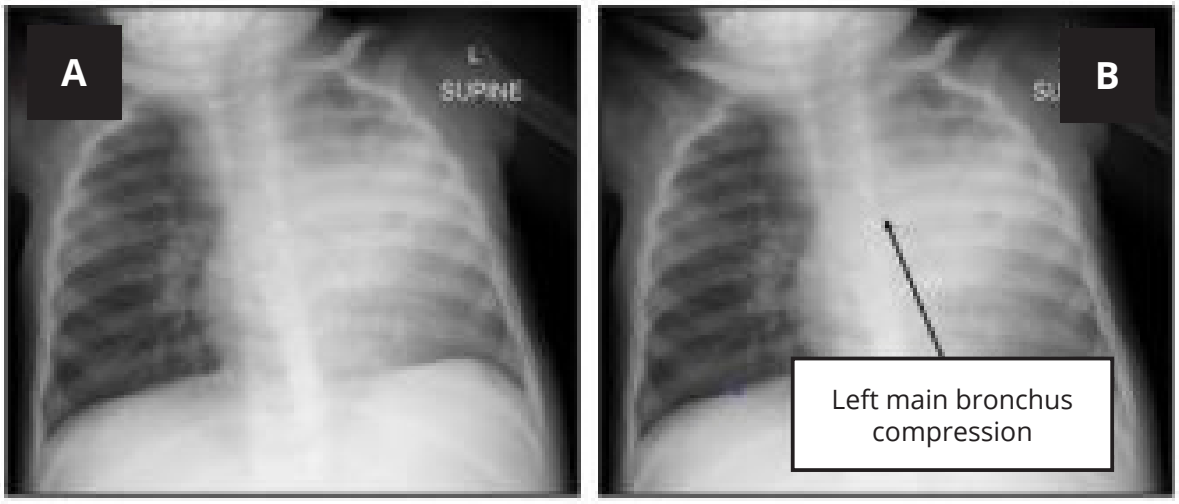
This CXR shows fine millet-sized nodules typically seen in miliary TB. The nodules are all of similar size and evenly spread throughout both lung fields. No other radiological signs of primary TB are visible. This indicates radiologically **severe** disease.



CXR taken from 3-year-old child. Note the right middle lobe opacification with breakdown (cavity formation). An enlarged left hilar node appears to be visible. This indicates radiologically **severe** disease.

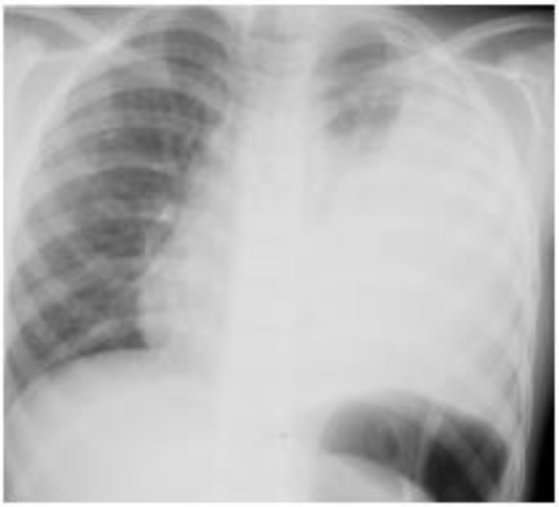


CXR (B) is an annotated version of CXR (A), which was taken from a 3-year-old child. Note that the right hilum appears full, with an outwardly bulging opacity that is suggestive of an enlarged right hilar lymph node. Note also the bilateral narrowing of the airways due to pressure exerted by the enlarged perihilar and sub-carinal lymph nodes on the airways. This indicates radiologically **severe** disease.

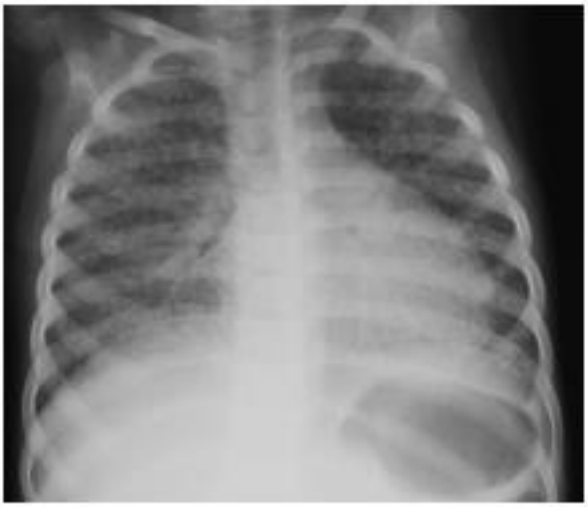


CXR (B) is an annotated version of CXR (A) showing dense lobar opacification on the left upper lobe with narrowing of the left main bronchus. This CXR shows the effect of enlarged lymph nodes on the bronchus causing narrowing of the airway. The enlarged lymph nodes are not clearly visible on the AP film but may be clear on a lateral film. This indicates radiologically **severe** disease.

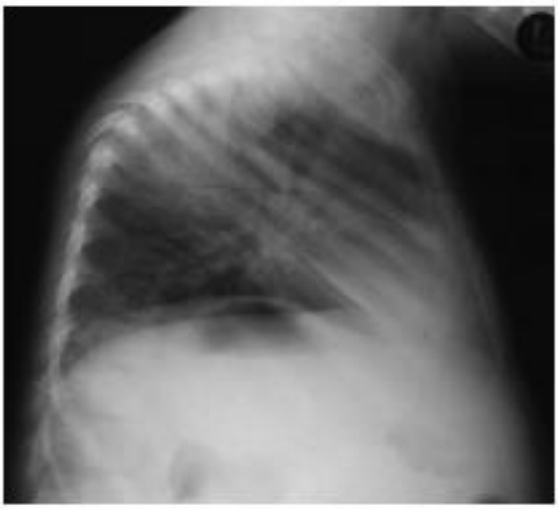
CXR abnormalities seen in children with EPTB



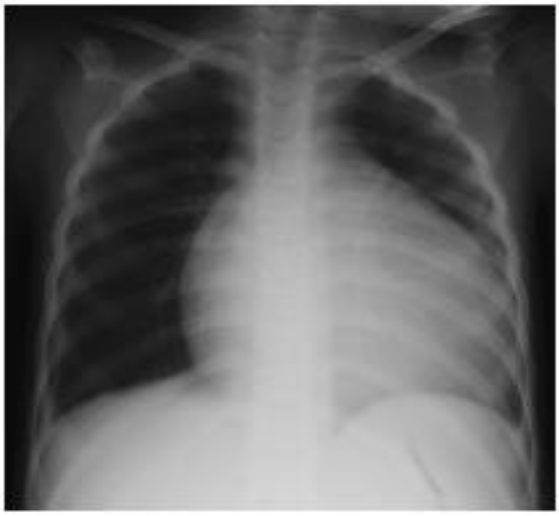
TB pleural effusion: large left-sided effusion; pleural tap advised to differentiate from empyema



Military TB: typical bilateral diffuse and micronodular pattern



Spinal TB: collapse of thoracic vertebra causing angulation



Pericardial TB: enlarged cardiac shadow; ultrasound advised to differentiate from other causes of cardiac failure

Source: International Union Against Tuberculosis and Lung Disease. Diagnostic CXR Atlas for Tuberculosis in Children: A Guide for Chest X-Ray Interpretation. Second Edition. Paris, France: The Union, 2022.

6.4.3 Additional investigations if extrapulmonary TB is presumed

Table 7 Investigations to diagnose extrapulmonary TB

Site of EPTB	Investigation	Comment
TB Meningitis	• Lumbar puncture to obtain CSF* for TB-NAAT, culture and biochemistry (See also Box 2 on page 27) • Neuroimaging** • CXR	• Usually young (<5 years) with disseminated disease and severely ill • CSF finding suggestive of TBM include leucocytosis with lymphocyte predominance, elevated protein and low CSF glucose • Children with miliary tuberculosis should all be considered to have meningitis, even if no symptoms or neurological signs are present and even if CSF has a normal result
Miliary TB	• CXR • Lumbar puncture	
TB Adenitis	• Fine-needle aspiration for TB-NAAT and histology • CXR	• Most common form of EPTB in children • If axillary node enlargement on the same side as the BCG in an infant, consider BCG disease
Pleural TB	• CXR • Ultrasound, if available • Pleural tap*	• Non-severe forms of TB lymphadenitis and pleural TB can be managed at the primary care level. • For non-severe forms of pleural TB, the diagnosis is usually made at a hospital level (to exclude other causes) but can be managed at the primary care level once the diagnosis is made. • Other forms of EPTB will usually require referral, with initial hospitalisation for further investigations and specific management, including specialist involvement.
Abdominal TB	• Ascitic tap • Ultrasound • CXR	
Pericardial TB	• CXR • Cardiac ultrasound • Pericardial tap	
Spinal TB	• X-ray spine ± other imaging of the spine (MRI or CT) • CXR	
TB of Bone and Joint	• X-ray or other imaging of bone/joint • Joint tap*	

* Typical findings: straw-coloured fluid, exudate with lymphocytic predominance and high protein; sample should be sent for rapid molecular diagnostic testing and culture.
** Depending on neurological signs, neuroimaging may be requested before lumbar puncture

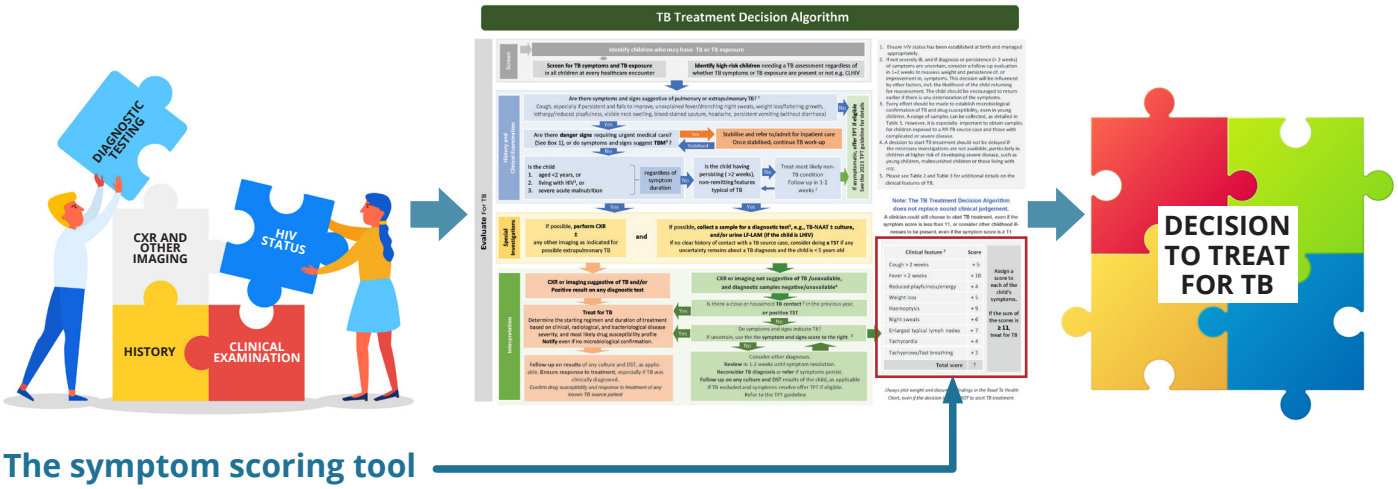
Abbreviations: BCG, bacille Calmette-Guérin; CXR, chest X-ray; CSF, cerebrospinal fluid; EPTB, extra-pulmonary TB; TB-NAAT, TB nucleic acid amplification test

Box 2 Recommendations for collection of cerebrospinal fluid samples

- If safe to do so, a lumbar puncture (LP) should ideally be done before treatment is initiated.
- Take as large a sample as possible, aiming for at least 5 ml, but more if feasible. This is not always obtained in younger children, and tests should be prioritised according to the volume of the sample obtained in the following order:
  - Chemistry, cell count, Indian Ink
    - The cell count and chemistry are more likely to yield a result indicating TBM than NAAT and culture.
  - Bacterial microscopy, culture and sensitivity
  - If the sample is sufficient (i.e. 3ml or more), request a TB-NAAT and TB culture (3ml sample). If the sample volume is low, i.e. 2ml or less – request TB-NAAT
    - Neither TB NAAT nor TB culture is especially sensitive on CSF. If positive, it gives a definite diagnosis, but negative tests on CSF do not exclude TB.
    - While NAAT allows rapid identification, only rifampicin sensitivity is reported. If the culture is positive, further NAAT DST, as well as phenotypic DST for any drug, can be done.
    - TB microscopy is not a priority in our setting due to negligible yields.
  - If there is a concern about focal lesions or the risk of coning, neuroimaging is the investigation of choice, and LP should be deferred.
  - Although the LP can be deferred, treatment for TBM should not be deferred if there is a strong clinical suspicion of TBM.

6.5 TB Treatment Decision Algorithm

Now that we have looked at the specific details of each puzzle piece in the preceding text, the **TB Treatment Decision Algorithm** in *Figure 6 on page 29* will help us interpret all the puzzle pieces together to decide whether to treat for TB or not.



The symptom scoring tool

The symptom scoring tool in the TB Treatment Decision Algorithm in *Figure 6 on page 29* aims to facilitate TB diagnosis, particularly at the PHC level, **where CXR and bacteriological testing may not be readily available**. It features only the signs and symptoms section based on the child's clinical history and physical examination. When a clinical feature is present, the corresponding score is noted, and the scores are added. A decision to start treatment is made based on a score **equal to or more than 11.**

Clinical feature	Score
Cough >2 weeks	+5
Fever >2 weeks	+10
Lethargy	+4
Weight loss	+5
Haemoptysis	+9
Night sweats	+6
Enlarged typical lymph nodes	+7
Tachycardia	+4
Tachypnoea/fast breathing	+2
Total score	?

For example:

- If a child has a cough for more than 2 weeks (+5 points), fever for 5 days (0 points as it is less than 2 weeks) and tachypnoea (+2 points), the child is assigned 7 points and should not start TB treatment. The child should be treated for the most likely alternative diagnosis and reassessed in 1–2 weeks.
- If a child has a cough for more than 2 weeks (+5 points), weight loss (+5 points) and swollen lymph nodes (+7 points), the child is assigned 17 points and should start TB treatment.

Remember:

- If necessary, obtain telephonic advice to facilitate decision-making.
- The TB Treatment Decision Algorithm guides decision-making but does not replace **clinical judgment.**
  - A clinician could still choose to start TB treatment, even if the symptom score is less than 11.
  - Many TB symptoms are non-specific: a clinician could still consider other common childhood illnesses, even if the symptom score is 11 or more.

A decision to start TB treatment should not be delayed if the necessary investigations are not available, particularly in children at higher risk of developing severe disease, such as young children, malnourished children or those living with HIV. If sufficient clinical or radiological evidence suggests TB, treatment may be started without bacteriological confirmation.

TB Treatment Decision Algorithm

Evaluate For TB

Screen

Identify children who may have TB or TB exposure

- **Screen for TB symptoms and TB exposure** in all children at every healthcare encounter
- **Identify high-risk children** needing a TB assessment regardless of whether TB symptoms or TB exposure are present or not e.g. CLHIV

History and Clinical Examination

Are there symptoms and signs suggestive of pulmonary or extrapulmonary TB? [1]

Cough, especially if persistent and fails to improve, unexplained fever/drenching night sweats, weight loss/faltering growth, lethargy/reduced playfulness, visible neck swelling, blood-stained sputum, headache, persistent vomiting (without diarrhoea)

NO → If asymptomatic, offer TPT if eligible See the 2023 TPT guideline for details

YES

Are there **danger signs** requiring urgent medical care? (See Box 1), or do symptoms and signs suggest **TBM**[1] ?

YES → Stabilise and refer to/admit for inpatient care Once stabilised, continue TB work-up

STABILISED → Once stabilised, continue TB work-up

NO

Is the child
1. aged <2 years, or
2. living with HIV[2], or
3. severely and acutely malnourished?

regardless of symptom duration

NO → Is the child having persisting (>2 weeks), non-remitting features typical of TB

NO → Treat most likely non-TB condition Follow up in 1-2 weeks [3]

YES

YES

Investigations

If possible, **perform CXR** ± any other imaging as indicated for possible extrapulmonary TB

and

If possible, **collect a sample for a diagnostic test**[4], **e.g., TB-NAAT ± culture, and/or urine LF-LAM (if the child is LHIV)**
If no clear history of contact with a TB source case, consider doing a TST if any uncertainty remains about a TB diagnosis and the child is < 5 years old

Interpretation

CXR or imaging suggestive of TB and/or Positive result on any diagnostic test

Treat for TB
Determine the starting regimen and duration of treatment based on clinical, radiological, and bacteriological disease severity, and most likely drug susceptibility profile.
Notify even if no microbiological confirmation.

Follow-up on results of any culture and DST, as applicable. **Ensure response to treatment,** especially if TB was clinically diagnosed.
Confirm drug susceptibility and response to treatment of any known TB source patient

CXR or imaging not suggestive of TB /unavailable, and diagnostic samples negative/unavailable[5]

Is there a close or household **TB contact**[3] in the previous year, **or positive TST**

YES

NO

Do symptoms and signs indicate TB?
If uncertain, use the the **symptom and signs score to the right.**

YES

NO

Consider other diagnoses.
Review in 1-2 weeks until symptom resolution.
Reconsider TB diagnosis or refer if symptoms persist.
Follow-up on any culture and DST results of the child, as applicable
If TB excluded and symptoms resolve offer TPT if eligible.
Refer to the TPT guideline

1. Please see Table 2 and Table 3 for additional details on the clinical features of TB.
2. Ensure HIV status has been established and managed appropriately.
3. If not severely ill, and if diagnosis or persistence (> 2 weeks) of symptoms are uncertain, consider a follow-up evaluation in 1-2 weeks to reassess weight and persistence of, or improvement in, symptoms. This decision will be influenced by other factors, incl. the likelihood of the child returning for reassessment. The child should be encouraged to return earlier if there is any deterioration of the symptoms.
4. Every effort should be made to establish microbiological confirmation of TB and drug susceptibility, even in young children. A range of samples can be collected, as detailed in Table 5. However, it is especially important to obtain samples for children exposed to a RR-TB source case and those with complicated or severe disease.
5. A decision to start TB treatment should not be delayed if the necessary investigations are not available, particularly in children at higher risk of developing severe disease, such as young children, malnourished children or those living with HIV.

Note: The TB Treatment Decision Algorithm does not replace sound clinical judgement.

A clinician could still choose to start TB treatment, even if the symptom score is less than 11, or consider other childhood illnesses to be present, even if the symptom score is ≥ 11

Clinical feature [1]	Score	
Cough > 2 weeks	+ 5	Assign a score to each of the child's symptoms. If the sum of the scores is **≥ 11**, treat for TB
Fever > 2 weeks	+ 10	
Reduced playfulness/energy	+ 4	
Weight loss	+ 5	
Haemoptysis	+ 9	
Night sweats	+ 6	
Enlarged typical lymph nodes	+ 7	
Tachycardia	+ 4	
Tachypnoea/fast breathing	+ 2	
Total score	?	

Always plot weight and document findings in the Road To Health Chart, even if the decision is made NOT to start TB treatment.

Figure 6 TB Treatment Decision Algorithm

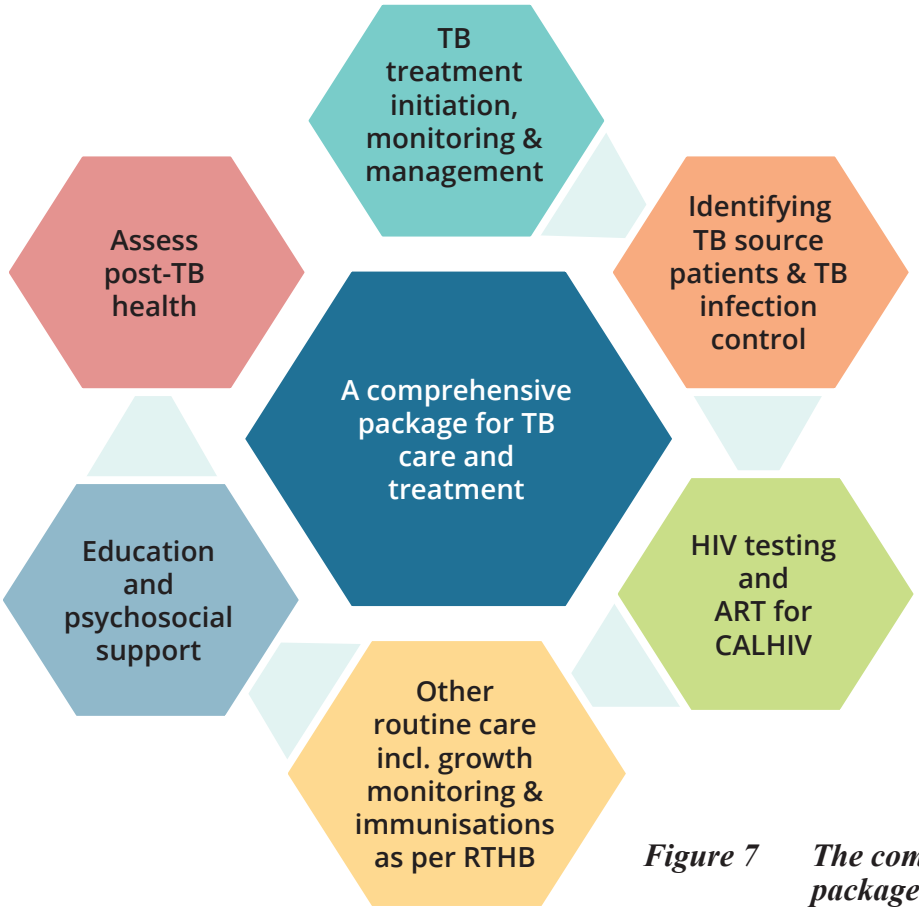
7 Overview of the components of a comprehensive package of care for TB

Once a decision has been made to treat for TB, the patient requires a comprehensive and patient-centred package of care that includes the following:

- Providing anti-TB treatment, including treatment initiation, monitoring and management to achieve the desired treatment outcomes (See *Sections 8 to 11* and *Section 14 on page 65*)
- Identifying adult TB source patients (and other child or adolescent contacts where appropriate) (See *Section 8.3 on page 38*)
- Preventing, diagnosing and managing co-morbid illnesses, e.g., HIV (See *Section 12 on page 58*)
- Providing other routine child and adolescent health care, including immunisations and growth monitoring, or contraception as appropriate (See *Section 8.4 on page 39*)
- Providing psychosocial support (See *Section 8.5 on page 40*)
- Assessing post-TB health (See *Section 16 on page 78*)

In addition, routine TB programme activities should be completed, including recording and reporting for monitoring and evaluation purposes (See *Section 15 on page 72*).

Delivery of all these care components should take a **patient-centred approach** as outlined in *Section 13 on page 63*. This requires effective communication and providing care in a coordinated and integrated manner, acknowledging that the TB episode being treated is only one component of the child's healthcare needs and the child's health needs are only one of the family's healthcare needs. The components of care are summarised in *Figure 7 on page 30* below.



Clinicians should provide TB management as part of an integrated package of care at clinical consultation visits. Failure to combine care leads to increased visit schedules and significantly increases the risk of disengagement and loss-to-follow-up (LTF).

Figure 7 The components of a comprehensive package of care for TB

8 Initiating TB Treatment

As illustrated in *Figure 8 on page 31*, the regimen prescribed for DS-TB should consider the following:

- whether treatment initiation is **urgent,** such as in the case of TBM.
- whether TB disease is categorised as **severe or non-severe** on the basis of clinical presentation and CXR abnormalities.
- what treatment **regimen** is indicated: drugs in the regimen will be determined by
  - drug susceptibility (DS-TB vs RR-TB)
  - the site of TB (neurological vs non-neurological sites)
- the **duration** the treatment regimen is prescribed, determined by:
  - an assessment of **disease severity** at the start of treatment to determine eligibility for the new shortened 4-month treatment regimen.
  - the **site of TB,** e.g. TB of the bone/joints require longer 12-month regimens
  - an assessment of **treatment response** at the end of treatment to determine if the child is eligible to end the new shortened treatment regimen after four months of treatment.
- whether there are **comorbidities**, such as HIV infection, severe malnutrition or severe anaemia, that require specific treatment.

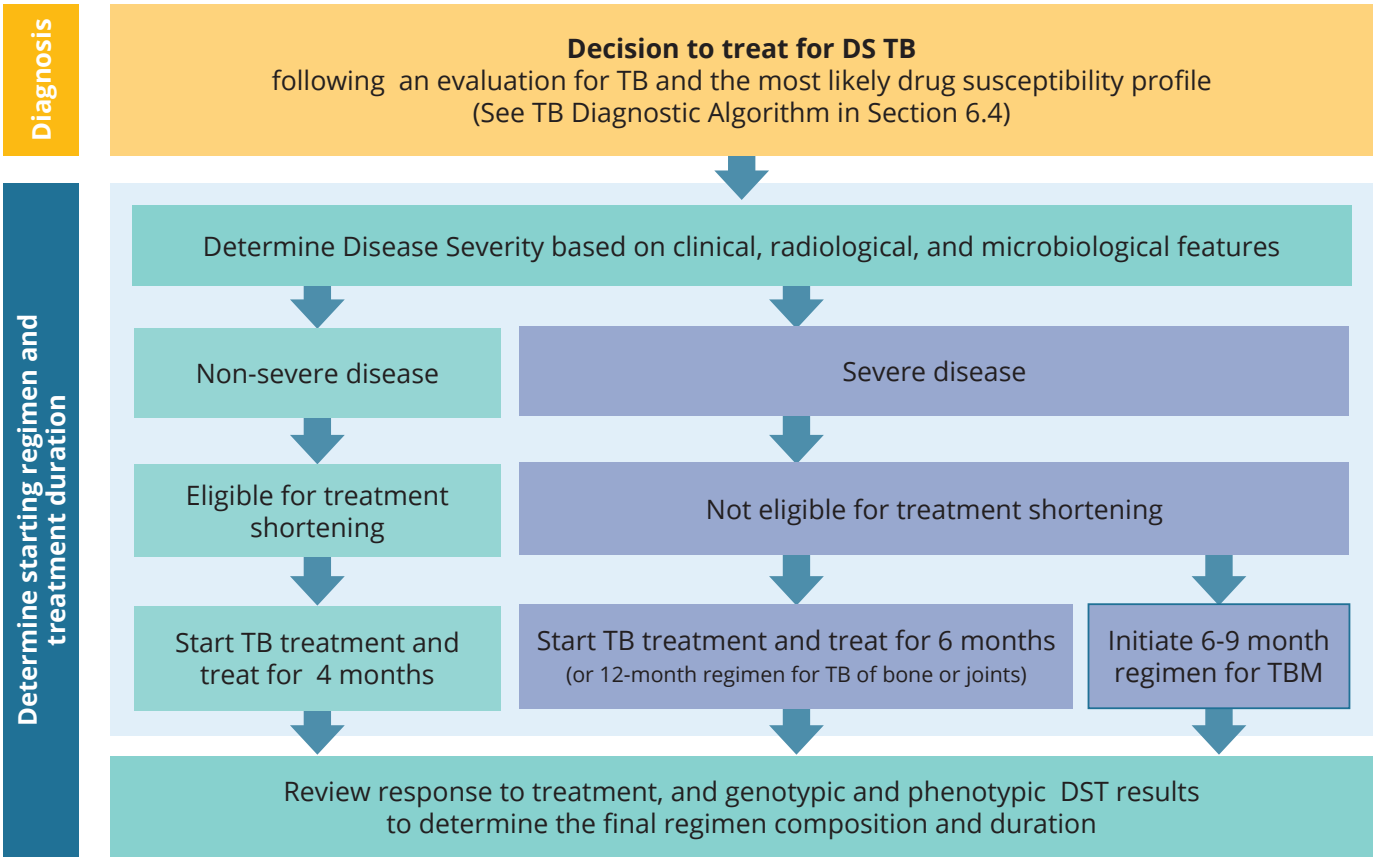


Figure 8 Determining the starting regimen and treatment duration

8.1 Assessing TB disease severity

- TB disease in children and adolescents ranges from non-severe to severe.
- Children with non-severe, pulmonary DS-TB and DS cervical TB lymphadenitis can be treated with the **shortened 4-month treatment regimen** provided they adhere to therapy and have an appropriate clinical response. This includes children and adolescents living with HIV (CALHIV) stable on ART who meet the eligibility criteria for ART and viral suppression (See ***section 8.1.1 below)***
- Children and adolescents with severe pulmonary disease, extrapulmonary disease (except isolated, cervical TB lymphadenitis), miliary TB and TBM are considered to have severe disease and are not eligible for shortened regimens.
- If uncertainty exists, provide a longer therapy course.
- There must be good communication between the different levels of care regarding the recommended treatment duration, especially for children who were managed initially at the hospital level, as healthcare providers at various levels need all the information to decide on treatment shortening.

8.1.1 Clinical TB disease severity

The following clinical factors must be considered to determine the severity of TB disease.[9]

Age of the child

- Very young children have a high risk of disseminated disease; therefore, children <3 months of age are not eligible for treatment shortening.
- Because older children (above approximately eight years of age) are more likely to have adult-type pulmonary TB, children ≥ 8 years can only be classified as having non-severe disease (and be eligible for treatment shortening) if a CXR is available.
- These guidelines do not apply to persons >16 years of age.

Characteristics of the TB episode

- Except for cervical TB lymphadenitis, all children with extrapulmonary and disseminated TB are considered to have severe disease and are not eligible for treatment shortening.
- Asymmetrical chest movement and asymmetric or persistent wheezing may indicate complex intrathoracic TB with airway involvement, and these children cannot be classified as having non-severe pulmonary disease and are not eligible for treatment shortening.
- Children with a previous history of TB treatment are not eligible for treatment shortening, regardless of the CXR or clinical features, as there may be underlying unidentified vulnerability (e.g., immune disorders, genetic susceptibility to TB) or post-TB lung disease. Given the increased risk of treatment failure and drug resistance, children and adolescents who have been previously treated for any form of TB should be treated with the full 6-month treatment regimen.

9 WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

HIV status

- Children with immune deficiency are more likely to have complex and disseminated disease, and their response to TB treatment may be delayed.
- CALHIV must meet the following additional criteria to be eligible for treatment shortening:
  - They should be on ART for at least three months with a viral load result of <1000 copies/mL at TB diagnosis or within the three months preceding their TB diagnosis.
  - If they are ≥ 8 years of age, they should meet the radiological criteria for non-severe disease on CXR. Additional management of CALHIV is discussed in *Section 12 on page 58*.

Clinical and Nutritional status

- Children presenting with danger signs indicating severe illness (see *Box 1 on page 8*) are not eligible for treatment shortening.
- Children with severe acute malnutrition are not eligible for treatment shortening as this indicates more severe/complex disease.

Box 3 Definition of severe acute malnutrition (SAM)

Weight-for-height Z-score (WHZ) <−3 OR Mid Upper Arm Circumference (MUAC) <11.5 cm

8.1.2 Radiological TB disease severity

- The CXR is an important tool for assessing pulmonary disease severity and identifying possible disseminated disease in children and adolescents.
- It should be obtained if at all possible. If a CXR at initial diagnosis is unavailable, an image taken within the first month of therapy can be used to assess the severity of radiological disease.
- In settings where a CXR is not available, only children between the ages of 3 months and eight years who do not have HIV and who have clinically non-severe disease are eligible for treatment shortening, provided that they meet the follow-up criteria for treatment response. The rationale for this is that children older than 8 are more likely to have adult-type lung disease, and children with HIV are at higher risk for complex TB.
- **Non-severe radiological disease** is defined as:
  - Uncomplicated intrathoracic lymph node TB without airway obstruction/compression or
  - Simple TB pleural effusion or
  - Consolidation/opacification that is less than one lobe of the lungs, without any cavities, and without a miliary pattern.
- A classification of **severe radiological disease** is made if ANY of the following are present:
  - Complicated intra-thoracic lymph node TB (i.e., including airway compression or deviation and/or hyperinflation or collapse)
  - Consolidation involving ≥ 1 lobe
  - Complicated pleural effusion (i.e., loculated effusion/empyema / associated pneumothorax)
  - Miliary infiltrates
  - Cavities
- The radiological features of non-severe and severe TB are illustrated in *Figure 9 on page 34*.

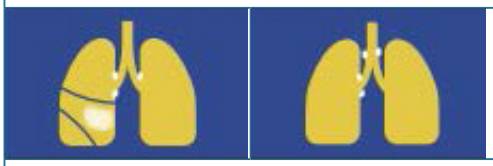
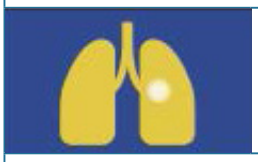
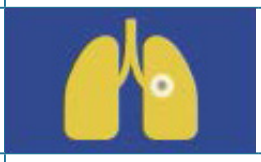
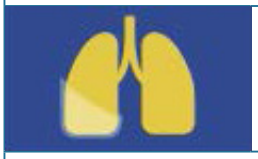
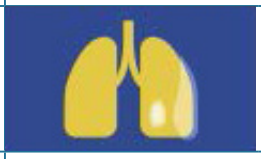
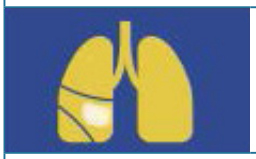
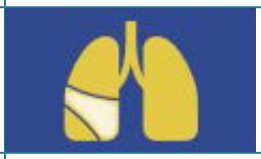
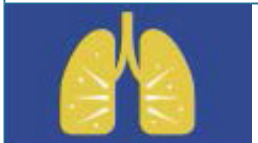
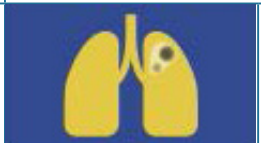
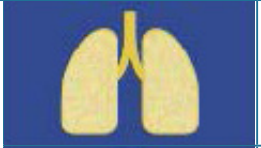
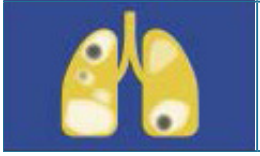
Non-Severe	Severe
Uncomplicaed lymph node disease	Complicaed lymph node disease
	
Primary (Ghon) focus	Primary (Ghon) focus with cavitation
	
Simple pleural effusion	Complicated pleural effusion
	
Alveolar opacification: < 1 lobe	Alveolar opacification: involving a whole lobe or multiple lobes
	
Other:	Other:
 Interstitial pneumonia	 All cavitary disease
 Perihilar infiltrates	 Expansile pneumonia
	 Miliary TB
	 TB Bronchopneumonia

Figure 9 Classification of radiological disease severity on CXR [10]

Note: alveolar opacification is also referred to as "consolidation"

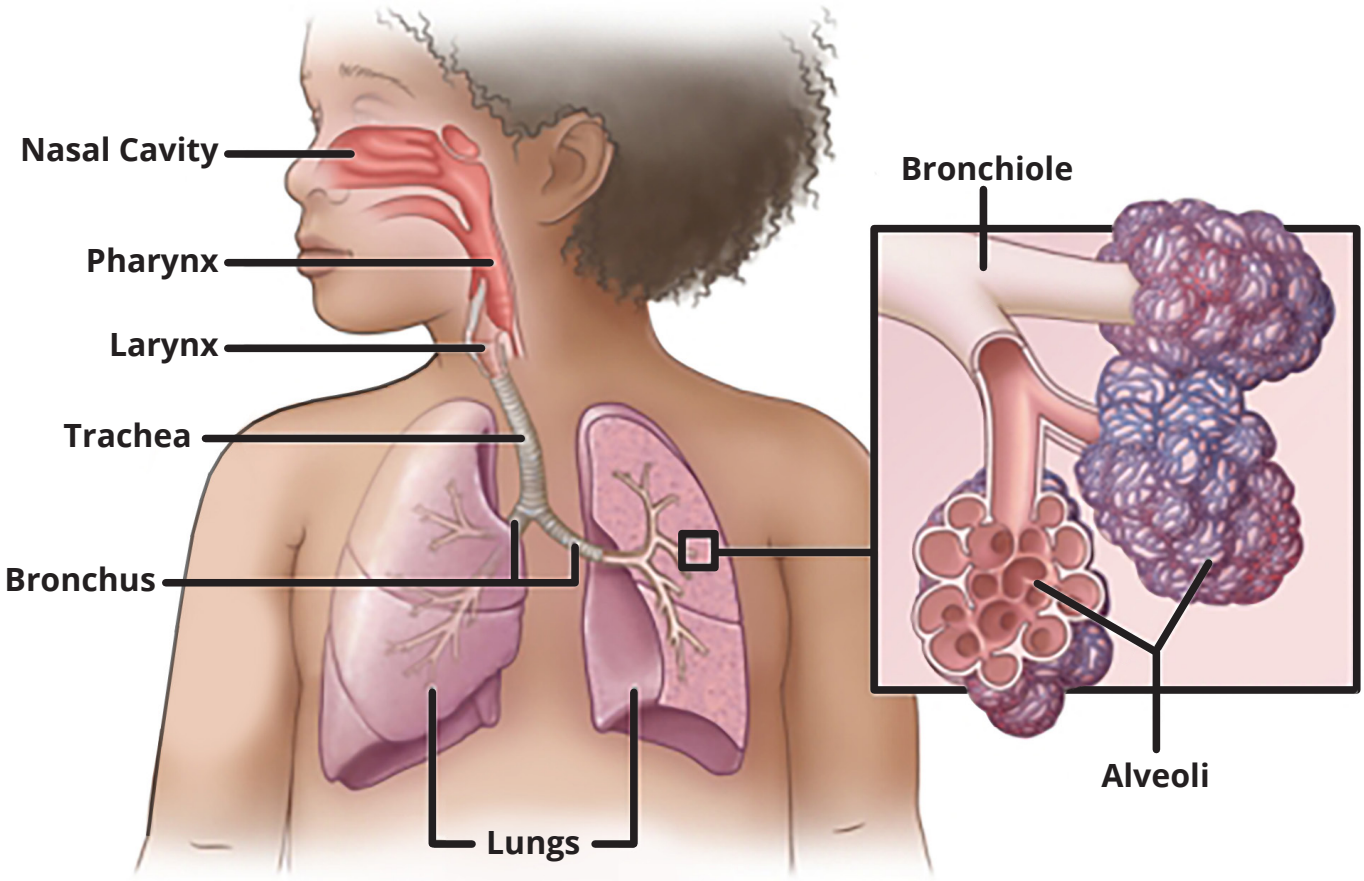
10 Palmer M, Seddon JA, Goussard P, Schaaf HS. Diagnostic CXR atlas for tuberculosis in children: A guide to chest X-ray interpretation, Second edition. Paris, France: International Union Against Tuberculosis and Lung Disease (The Union); 2022.

A detailed approach to CXR interpretation in child and adolescent TB is outlined in the Union's *Diagnostic CXR Atlas for Tuberculosis in Children*. https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children

8.1.3 Bacteriological TB disease severity

- Healthcare workers should always attempt to obtain bacteriological confirmation of TB in patients.
- A positive TB NAAT (e.g., Xpert MTB/RIF or Xpert MTB/RIF Ultra) and/or culture-positive TB result in isolation does not indicate severe disease. Other clinical and radiological features of disease severity must be assessed.
- A fine needle aspirate or tissue biopsy with a positive AFB smear in isolation does not indicate severe disease. Other clinical and radiological features of disease severity must be assessed.
- Smear microscopy tests are not routinely performed on the respiratory specimens of children; however, if a sputum or other respiratory sample smear microscopy test is positive for AFB, it indicates a high bacillary load and is classified as severe disease.

The criteria for eligibility for treatment shortening at diagnosis and follow-up, and with and without access to CXR, are summarised in *Figure 10 on page 36* and *Figure 11 on page 37*.



Assessing eligibility of children and adolescents for shortened TB treatment regimen

Scenario 1: CXR Available

DIAGNOSIS

Clinical Criteria

Eligible for treatment shortening if ALL OF THE BELOW CRITERIA ARE MET:

- Age 3 months to < 16 years at start of TB treatment
- Drug-susceptible pulmonary TB or cervical TB lymphadenitis (presumed or confirmed with no evidence of extrapulmonary TB other than lymphadenitis)
- First episode of TB (no previous TB treatment)
- No danger signs indicating severe illness at presentation (Box 1)
- No severe acute malnutrition
- No asymmetric or persistent wheezing
- If living with HIV: viral load < 1,000 in the preceding 3/12 AND on ART for > 3/12
- No respiratory sample that is AFB smear positive[1]

Radiological Criteria

Eligible for treatment shortening if NONE OF THE FOLLOWING ARE PRESENT:

- Complicated intra-thoracic lymph node TB (i.e., airway compression or deviation and / or hyperinflation or collapse)
- Consolidation ≥ 1 lobe
- Complicated pleural effusion (loculated effusion, empyema or pneumothorax)
- Miliary pattern
- Cavities

FOLLOW-UP

Clinical Criteria

Eligible for shorter treatment if ALL BELOW CRITERIA ARE MET:

- **Adherent** to treatment
- **MONTH 1:** All TB signs & symptoms improved
- **MONTH 4:** All TB signs & symptoms resolved[2] and appropriate/improving weight trend

If* not eligible *for the shortened treatment regimen, treat for standard duration (Table 8)

1 *Routine smears for AFB are not recommended as part of the diagnostic work-up. However, if there is an AFB smear positive result on any respiratory sample, the child is not eligible for treatment shortening. FNA smear positivity is not an exclusion.*

2 *If cervical peripheral lymph nodes did not decrease in size at month 4, continue to 6 months of treatment. If there was not a significant reduction in size of the lymph nodes, enlargement or complications, especially if TB was not bacteriologically confirmed, refer for further investigation (biopsy or aspiration) to exclude other diagnoses.*

Figure 10 Assessing children and adolescents' eligibility for treatment shortening when CXR is available

Assessing eligibility of children and adolescents for shortened TB treatment regimen

Scenario 2: No CXR Available

DIAGNOSIS — **Clinical Criteria**

Eligible for treatment shortening if ALL OF THE BELOW CRITERIA ARE MET:

- Age 3 months to **< 8 years** at start of TB treatment
- Drug-susceptible pulmonary TB or cervical TB lymphadenitis (presumed or confirmed with no evidence of extrapulmonary TB other than lymphadenitis)
- First episode of TB (no previous TB treatment)
- No danger signs indicating severe illness at presentation (Box 1)
- No severe acute malnutrition
- No asymmetric or persistent wheezing
- **Not living with HIV (HIV negative)**
- No respiratory sample that is AFB smear positive[1]

FOLLOW-UP — **Clinical Criteria**

Eligible for shorter treatment if ALL BELOW CRITERIA ARE MET:

- **Adherent** to treatment
- **MONTH 1:** All TB signs & symptoms improved
- **MONTH 4:** All TB signs & symptoms resolved[2] and appropriate/improving weight trend

If* not eligible *for the shortened treatment regimen, treat for standard duration (Table 8)

1 *Routine smears for AFB are not recommended as part of the diagnostic work-up. However, if there is an AFB smear positive result on any respiratory sample, the child is not eligible for treatment shortening. FNA smear positivity is not an exclusion.*

2 *If cervical peripheral lymph nodes did not decrease in size at month 4, continue to 6 months of treatment. If there was not a significant reduction in size of the lymph nodes, enlargement or complications, especially if TB was not bacteriologically confirmed, refer for further investigation (biopsy or aspiration) to exclude other diagnoses.*

Figure 11 Assessing children and adolescents' eligibility for treatment shortening when no CXR is available

8.2 Providing HIV testing and care

Appropriate HIV care is essential to reduce the morbidity and mortality of children and adolescents living with HIV and TB.

HIV impacts the natural progression of TB and TB treatment in the following ways:

- CALHIV are at a higher risk of developing TB disease.
- CALHIV may have more rapid TB disease progression and are at higher risk of developing severe disease.
- CALHIV and TB are at highest risk of death if not treated.

TB impacts HIV management in several ways. It affects:

- The timing of ART initiation.
- Antiretroviral drug selection in patients already on ART when TB treatment is initiated.
- Drug levels, due to significant drug interactions with rifampicin that reduce ART concentrations in the blood.
- Adherence, due to increased pill burden.
- Side effects due to overlapping toxicities, e.g. hepatic toxicity.

Therefore, every child or adolescent being treated for TB should have their HIV status determined and managed appropriately

In a TB/HIV co-infected patient, TB cannot be treated without also treating HIV, and HIV cannot be treated without also treating TB!
All CALHIV must receive a comprehensive, integrated and family-centred package of care for TB/HIV co-infection as detailed in Section 12.

8.3 Identifying adult TB source patients and implementing infection control

- Children with TB usually contract the disease from an infectious adult with TB.
- Therefore, it is important to find the source of infection and any other child contacts, where appropriate, to prevent further TB transmission.
- When a child is diagnosed with any form of TB, the parents and other household members (if not already on TB treatment) should be evaluated to identify any potential source patient with undiagnosed TB.
- Children with TB usually have paucibacillary disease and pose a low infection risk to adults and other children. However, children or adolescents who are AFB smear-microscopy or TB NAAT positive or who have cavities on CXR may be contagious.
- Older children (typically children eight years and older) and adolescents tend to develop adult-type pulmonary TB (PTB), frequently with higher bacillary load and pose higher infection risk to others.
- All close contacts should be evaluated for TB symptoms, and where TB disease is excluded, appropriate TPT should be provided. For older children and adolescents it is important to consider the school environment for screening, specifically students in the same classroom. Screening should include disease specific education for the students, and utmost care should be taken to protect the patient's confidentiality to avoid stigmatization.
- Refer to the most recent South African National TB Programme TB Preventive Therapy Guidelines.

- Older children, parents, caregivers, and teachers should receive advice (See ***Box 4 below***) on preventing TB spread by an infectious patient, whether the TB source patient or an infectious older child.
- Children who receive effective treatment can resume school and social activities.

Box 4 Measures to prevent TB transmission in the home

- Instruct patients to cover their mouth and nose with their sleeve or a tissue when coughing or sneezing. After that, they should wash their hands and throw their tissue in the bin.
- Windows and doors must be kept open (weather permitting) to increase the ventilation and dilution of infectious particles in the house.
- Where possible, sleep alone and not in a room with other household members.
- During the first two weeks of treatment when the patient is still considered infectious:
  - Give patients surgical masks and advise them to wear them at home, during transportation and medical consultations.
  - Refrain from having visitors in the home.
- Patients are no longer infectious after two weeks of appropriate TB treatment.

Source: National Infection Prevention and Control Guidelines for TB, MDR-TB and XDR-TB, 2015

8.4 Providing other routine care and nutritional support as per the RTHB

- Ensure that all vaccinations are up to date
- Deworm and provide Vitamin A if appropriate and document in RTHB
- Children with TB frequently present with failure to thrive and weight loss (See ***Box 5 on page 39***). They, therefore, require a thorough clinical and nutritional evaluation at the start of treatment. This should include:
  - Measuring the weight, height and mid-upper arm circumference
  - Observing for signs of malnutrition, including oedema, severe wasting, or other vitamin or trace element deficiencies
- Energy needs increase in children with TB by 20 – 30%, depending on the age and growth status at assessment. It is important to advise the caregiver on how to meet the additional energy needs using food available at home. Where this is not possible, nutritional supplements should be provided.
- Children with severe malnutrition require urgent therapeutic feeding, and referral for nutritional support should be considered. Breastfeeding should be encouraged for all mothers still able to breastfeed.
- Provide adolescents with contraception and other sexual and reproductive health services as appropriate.

Box 5 The link between TB and malnutrition

- TB and malnutrition are closely linked because:
  - malnutrition results in the reduction of cell-mediated immunity, thereby increasing the risk of TB disease after infection, and
  - the catabolic effect of the TB disease results in weight loss and wasting, worsening the malnutrition.

8.5 Providing patient education and psychosocial support

TB is still associated with stigma and loss of income. Therefore, every child, adolescent and family being treated for TB should receive information, education, and emotional support to alleviate fear and anxiety. The clinician should communicate in a way that enhances the healthcare worker-patient relationship and improves adherence. Good patient education results in:

- An informed patient/caregiver
- An empowered patient/caregiver
- A less fearful patient/caregiver
- Better treatment outcomes

The following topics should be covered:

- The basic principles of TB disease and treatment.
- When to return for routine follow-up.
- TB infection prevention and control.
- Drug adverse effects, and to seek immediate care if the child develops jaundice, abdominal pain, or vomiting.
- The importance of adherence to TB treatment.

Also, reassure the family that:

- Most children and adolescents with TB are successfully cured.
- The healthcare team is there to answer their questions.
- Family members should be involved in treatment decisions.
- All the relevant information regarding the child's TB diagnosis and treatment is documented in the Road-to-Health booklet. It is, therefore, important to always take this along for any healthcare visits.

If available, resources for nutritional or financial support should be provided. Social grants should be requested for families with children affected by TB.

9 Treating all forms of drug-susceptible PTB and EPTB (excluding TBM, other forms of CNS TB and miliary TB)

- The TB treatment regimen should be continued until completion unless an alternative diagnosis has been confirmed.
- Therapeutic trials of TB treatment are not recommended.
- Each TB treatment episode should be entered into the TB treatment register and reported to the TB programme.

9.1 Antituberculosis medication

Treatment of pulmonary and extrapulmonary DS-TB:

The treatment principles of DS-TB in children are similar to those used in adults. Treatment consists of 2 phases:

- **An intensive phase** of 2 months consisting of 4 drugs:
  - isoniazid, rifampicin and pyrazinamide, and
  - a fourth drug: either ethambutol in most, or ethionamide
    - ethambutol will be used in most children, but ethionamide can be considered in infants younger than three months or weighing < 3kg, given the challenges with ethambutol administration and monitoring for ocular toxicity in the very young.

- A **continuation phase** consisting of 2 drugs:
  - Isoniazid and rifampicin

All children and adolescents with DS-TB (excluding TBM, other forms of CNS TB and miliary TB) will initiate the same intensive phase of TB treatment using four anti-TB medications. However, the duration of the continuation phase depends on the eligibility for treatment shortening, the site of TB and the response to therapy:

- In the patient with non-severe PTB and/or cervical TB lymphadenitis, the continuation phase is two months, provided the child meets the eligibility criteria for treatment shortening at initial diagnosis and has an appropriate clinical response (See *Figure 10 on page 36* and *Figure 11 on page 37*)
- Children with PTB and EPTB who did not meet the initial criteria for non-severe disease should receive a minimum of 4 months continuation phase. The clinical response should be reviewed, and the continuation phase can be extended, if needed, to 7 months on an individual basis.
- In children with bone and joint TB, the duration of the continuation phase is typically prolonged up to 10 months, or even longer in specific circumstances in consultation with a specialist.
- For treatment of miliary TB, TBM, and other forms of CNS-TB, see *Section 10 on page 44*.
- TB drugs are dosed in weight bands and should be adjusted as the child grows.
- *Table 8 on page 42* provides detailed information on treatment duration and weight-banded drug dosages.

Table 8 Drug dosing chart for children and adolescents with drug-susceptible TB

2023 TB Drug Dosing Chart for Children / Adolescents <16 years

With Confirmed or Clinically Diagnosed Drug-Susceptible Non-severe TB, Severe Pulmonary TB and Extrapulmonary TB

excluding TB meningitis / central nervous system (CNS) TB / miliary TB (refer to chart on next page)

	Intensive phase Once daily, 7 days a week		Continuation phase Once daily, 7 days a week			
	Duration 2 months		Non-severe TB Duration: 2 months	Severe PTB & most EPTB: Duration: 4 months	Bone & joint TB: Duration: 10 months	
Target dose (dose range) (mg/kg/day)	Isoniazid (H): 10 (7-15), Rifampicin (R): 15 (10-20), Pyrazinamide (Z): 35 (30-40), Ethambutol (E): 20 (15-25)					Target dose (dose range) (mg/kg/day)
Formulation Body weight (kg)	HRZ 50/75/150 mg dispersible tablet (scored) OR 50/75/150 mg/4 ml suspension ♦	E 400 mg tablet (not scored) OR 400 mg/8 ml suspension #	HR 50/75 mg dispersible tablet (scored) OR 50/75 mg/4 ml suspension ♦			Formulation Body weight (kg)
<2	Obtain expert advice					<2
2 - 2.9	½ tab	1 ml	½ tab			2 - 2.9
3 - 3.9	¾ tab (3 ml) ♦	1.5 ml	¾ tab (3 ml) ♦			3 - 3.9
4 – 7.9	1 tab	2.5 ml	1 tab			4 – 7.9
8 - 11.9	2 tabs	½ tab or 4 ml	2 tabs			8 - 11.9
12 - 15.9	3 tabs	¾ tab or 6 ml	3 tabs			12 - 15.9
16 - 24.9	4 tabs	1 tab or 8 ml	4 tabs			16 - 24.9
≥ 25	HRZE 75/150/400/275 mg tablet		Choose one of below options			≥ 25
			HR 75/150 mg tablet	HR 150/300 mg tablet		
25 – 29.9	2 tabs		2 tabs	1 tab		25-29.9
30 – 34.9	3 tabs		3 tabs	-		30 – 34.9
35 – 64.9	4 tabs		4 tabs	2 tabs		35 – 64.9
≥65	5 tabs		5 tabs	-		≥65

Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication

♦ To make an oral suspension, for weight band 3 – 3.9 kg, for each dose, disperse 1 x HRZ 50/75/150 mg tablet (2 months intensive phase) or 1 x HR 50/75 mg tablet (continuation phase) in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5-10 ml) and administering all of the the suspension to the child orally or via nasogastric tube.

If oral suspension required, for each dose, crush 1 x Ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml), administer required dose as indicated in above chart, discard unused suspension.

Adapted from World Health Organisation Operational Handbook on Tuberculosis Module 5: Management of tuberculosis in children and adolescents (2022)

9.2 Supplemental pyridoxine

Isoniazid may cause symptomatic pyridoxine deficiency in certain at-risk patients. This can lead to peripheral neuropathy. Supplemental pyridoxine is therefore recommended in the following populations:

- Malnourished children
- CALHIV
- Breastfed infants
- Children or adolescents older than eight years
- Children receiving high-dose INH (as with TBM/miliary TB)

The recommended oral dosage for supplemental pyridoxine is:

- < 5 years: 12.5 mg/day (½ tablet)
- ≥ 5 years: 25 mg (1 tablet)

9.3 The use of corticosteroids in children with TB

The evidence for the use of corticosteroids in children with PTB and EPTB is limited. Oral corticosteroids should be considered in children with the following forms of TB:

- Intra-thoracic lymphadenopathy with significant airway compression.
- TB immune reconstitution inflammatory syndrome (IRIS).
- TBM (refer to *Section 10.1 on page 44*)
- Tuberculoma or pseudo-abscess with surrounding brain oedema.
- Pericarditis – studies in adults suggest that this may not be beneficial.

The recommended dose is prednisone 2 mg/kg orally, daily for four weeks (maximum daily dose 60mg). The dose should be tapered to stop over two weeks (a total of six weeks, including the tapering period).

10 Treating TBM, other forms of CNS TB and miliary TB

Treatment of tuberculous meningitis (TBM) has the following components:

- Treatment regimens to kill the mycobacteria
- Prevention of stroke/infarctions and reducing inflammation
- Managing hydrocephalus
- Supportive care

10.1 Treatment regimens for presumed or confirmed DS-TBM

Treatment for drug-susceptible TBM should include the following four drugs: isoniazid, rifampicin, pyrazinamide, and ethionamide, using the weight-banded dosing outlined in *Table 9 on page 45*. If TB drug resistance is presumed or confirmed, consult the guidelines for drug-resistant TB and experts for guidance on management.

Children and adolescents without HIV

- The duration of therapy is six months, and all four drugs should be used for the full six months.
- In children with complex disease, where treatment interruptions or changes occurred, or in children with other significant immune dysfunction, the treatment duration can be extended to 9 months or longer. If there is uncertainty about the duration of treatment in these children, an expert should be consulted.

Children and adolescents living with HIV

- Children living with HIV not on antiretroviral therapy (ART) should delay initiation of ART for at least four weeks to reduce the risk of TB-IRIS.
- Children living with HIV and already on ART require:
    - Review of adherence to ART and identification of virological failure
    - HIV viral load should be performed if on treatment longer than three months and the previous viral load is more than three months before the diagnosis of TBM. Further viral loads should be based on the result as well as current HIV treatment guidelines.
    - Adjustment of drugs/doses of ART where appropriate, including for drug-drug interactions and virological failure.
- There are no data to guide the duration of treatment with the current regimen in children living with HIV. Expert recommendation is for treatment for nine months, with all four drugs being used for the full nine months. An expert should be consulted if unsure of treatment.

Table 9 Drug dosing chart for treatment of DS-TBM, CNS TB and miliary TB

2023 TB Drug Dosing Chart for Children / Adolescents <16 years

With Confirmed/Presumed Drug-Susceptible TB Meningitis / Central Nervous System TB / Miliary TB

	Single phase of treatment: 6-9 months Once daily, 7 days a week			
Target dose range & maximum doses	Isoniazid (H): 15-20 mg/kg, maximum dose 450 mg Rifampicin (R): 22.5-30 mg/kg, maximum dose 900 mg	Pyrazinamide (Z): 35-45 mg/kg, maximum dose 2 g	Ethionamide (Eto): 17.5-22.5 mg/kg, maximum dose 1 g	Target dose range & maximum doses
Formulation Body weight (kg)	HR 50/75 mg dispersible tablet (scored) OR 50/75 mg/4 ml suspension ♦	Z 500 mg tablet (scored) OR 500 mg/8 ml suspension ∞	Eto 250 mg tablet (not scored) OR 250 mg/8 ml suspension #	Formulation Body weight (kg)
<2	Obtain expert advice			<2
2 – 2.9	¾ tab (3 ml) ♦	1 ml	1.5 ml	2 – 2.9
3 – 3.9	1 ½ tabs	2 ml	2 ml	3 – 3.9
4 – 4.9	<3 months: 1 ½ tabs ≥3 months: 2 tabs	2.5 ml	2.5 ml	4 – 4.9
5 – 5.9	2 ½ tabs	3 ml	3 ml	5 – 5.9
6 - 7.9	3 tabs	½ tab or 4 ml	½ tab or 4 ml	6 – 7.9
8 - 8.9	3 ½ tabs			8 - 8.9
9 – 9.9		¾ tab or 6 ml	¾ tab or 6 ml	9 – 9.9
10 – 11.9	4 tabs			10 – 11.9
12 – 12.9		1 tab or 8 ml	1 tab or 8 ml	12 – 12.9
13 – 14.9	4 ½ tabs			13 – 14.9
15 – 15.9	5 tabs		1 ¼ tabs or 10 ml	15 – 15.9
16 - 16.9	6 tabs			16 - 16.9
17 – 17.9		1 ¼ tabs or 10 ml		17 – 17.9
18 – 19.9			1 ½ tabs or 12 ml	18 – 19.9
20 – 24.9	7 tabs	1 ½ tabs		20 – 24.9
25 – 29.9	**HR 150/300 mg tablet:** 3 tabs	2 tabs	2 tabs or 16 ml	25 – 29.9
30 – 34.9		2 ½ tabs	2 ½ tabs or 20 ml	30 - 34.9
35 – 39.9		3 tabs	3 tabs or 24 ml	35 – 39.9
40 – 49.9		3 ½ tabs	3 ½ tab or 28 ml	40 – 49.9
≥50		4 tabs	4 tabs or 32 ml	≥50

Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication if possible

♦ To make an oral suspension for weight band 2 - 2.9 kg, for each dose, disperse 1 x HR 50/75 mg tablet in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5-10 ml) and administering all of the the suspension to the child orally or via nasogastric tube.

∞ To make an oral suspension, crush 1 x 500 mg Pyrazinamide tablet to a fine powder, disperse in 8 ml water to prepare a concentration of 500 mg/8 ml (62.5 mg/ml), administer required dose as indicated in above chart, discard unused suspension.

To make an oral suspension, crush 1 x 250 mg Ethionamide tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 250 mg/8 ml (31.3 mg/ml), administer required dose as indicated in above chart, discard unused suspension.

Adapted from World Health Organisation Operational Handbook on Tuberculosis Module 5: Management of tuberculosis in children and adolescents (2022)

10.2 Prevention of stroke and anti-inflammatory therapy

- All children with presumed TBM should initially be hospitalised. Twenty-five per cent of children who present without a stroke will develop infarctions in the first month of treatment.
- All children should receive oral prednisone 2 mg/kg/day (maximum dose 60 mg) for one month, followed by a 2-week weaning period. If it is difficult to distinguish between bacterial and TBM and the child requires corticosteroids because of the concern for severe raised intracranial pressure, dexamethasone 0.15 mg/kg/dose six hourly IVI can be used initially, followed by a switch to oral prednisone.
- Routine use of proton-pump inhibitors is not recommended to prevent gastritis. Give oral corticosteroids soon after a meal/feed to prevent steroid-induced gastritis.
- There is no evidence for routine use of other anti-inflammatory or anti-coagulation strategies. [11, 12, 13]

10.3 Managing hydrocephalus

- As far as possible, the neurosurgical team or a paediatric neurologist should review all children with hydrocephalus.
- All children with non-communicating hydrocephalus will require a neurosurgical intervention. The decision on the exact nature of the intervention will be determined by local capacity and expertise.
- Children with communicating hydrocephalus should be initiated on
    - Furosemide (1 mg/kg/day divided into two doses, maximum 40mg per dose) and
    - Acetazolamide (50 mg/kg/day) 6-hourly per os (maximum 2 grams per day).
    - This has been shown to normalise the intracranial pressure within seven days in most children, but not all. The duration of diuretic therapy is one month.
- The local management teams can consider additional strategies for monitoring and managing communicating hydrocephalus. These include repeated lumbar punctures with pressure monitoring, repeated CT scanning, endoscopic third ventriculostomy, and temporary extra-ventricular drainage. [12, 13]

10.4 Supportive care for children with TBM

- All children with TBM should initially be hospitalised, regardless of their clinical stage.
- Regular assessment of the neurological status, including respiratory rate and pattern, pulse rate and blood pressure, level of consciousness and posture, and oxygen saturation, as well as assessment for focal neurological features, including abnormal pupil responses, should be performed.
- The clinical situation should guide the frequency of monitoring. [13, 14]
- A deterioration in the level of consciousness could indicate worsening hydrocephalus, hyponatraemia, new brainstem infarction or cerebral oedema. Repeat imaging and urgent review of serum sodium should be considered. Management should target the likely cause of deterioration.

11 Solomons RS, van Toorn R, Cresswell FV, Seddon JA. Update on the Treatment of Pediatric Tuberculous Meningitis. Pediatr Infect Dis J. 2022;41(9):e393-e5. doi: 10.1097/INF.0000000000003557. PubMed PMID: 35421048.

12 Donovan J, Figaji A, Imran D, Phu NH, Rohlwink U, Thwaites GE. The neurocritical care of tuberculous meningitis. Lancet Neurol. 2019;18(8):771-83. doi: 10.1016/S1474-4422(19)30154-1. PubMed PMID: 31109897.

13 Huynh J, Abo YN, du Preez K, Solomons R, Dooley KE, Seddon JA. Tuberculous Meningitis in Children: Reducing the Burden of Death and Disability. Pathogens. 2021;11(1). doi: 10.3390/pathogens11010038. PubMed PMID: 35055986; PMCID: PMC8778027.

- Children with reduced levels of consciousness should be nursed with attention to:
    - Providing the highest level of monitoring available in the local setting
    - Airway protection and preventing aspiration
    - Positioning of the patient with raised upper body and head in the midline, where appropriate
    - Detecting and managing hypoxia
    - Preventing, detecting, and managing hypoglycaemia
    - Monitoring blood pressure
    - Correct placement of the nasogastric feeding tube
    - Providing pain relief and control fever
- Normal intravascular volume should be maintained. Avoid fluid restriction, and asses the fluid status every day.
- Cerebral oedema and raised intracranial pressure not related to hydrocephalus may require osmotic therapy. Hypertonic saline or mannitol can be used. Individual patient considerations would guide the choice. Hypertonic saline is increasingly preferred in neurocritical care because mannitol is more likely to decrease the intravascular volume, and low sodium is often present.
- Low serum sodium occurs in up to 65% of children with TBM and is related to the disease severity. Hyponatraemia can precipitate seizures and deepening coma, especially when the serum sodium drops to <125 mmol/L. Serum sodium <120 mmol/L is life-threatening.
- Low serum sodium can be due to either:
    - the syndrome of inappropriate antidiuretic hormone (SIADH) causing fluid retention and sodium dilution or
    - cerebral salt wasting causing sodium loss and hypovolemia
- The management of hyponatremia depends on the acuity, putative cause, severity and presence of symptoms. Although this is an important component of care, there are no randomised studies to guide management. The overlapping symptoms of low serum sodium and meningitis further complicate decision-making. Treating the low sodium can also lead to complications, as too rapid correction of low sodium may result in osmotic demyelination syndrome.
- The goal of therapy is to prevent further decreases in sodium, to decrease the possible cerebral oedema associated with reduced sodium, and to address symptoms of low sodium. ***Table 10 on page 48*** guides the management of hyponatremia in children with TBM. If there is uncertainty, discussion with an experienced clinician is recommended. Local recommendations and guidelines should always be considered. Normal hydration should be maintained, and dehydration should be avoided. When correcting serum sodium, total fluid requirement and glucose control should also be considered. This is particularly important for intravenous correction.

Table 10 Management of serum sodium in children with TBM

Classification of hyponatraemia/low serum sodium	Definition mmol/L	Action
Normal	135 – 145	None needed – continue normal fluid intake
Mild	130 – 134	Review hydration status carefully and consider repeating after 24 hours if it remains clinically stable.
Moderate	120 –129	Intravenous correction is usually needed: correction at 4 mmol/L over 24 hours. If neurological symptoms associated with low sodium occur, an initial bolus of 3 mL/kg over 1 hour of 3% saline can be considered. If chronic hyponatraemia occurs, oral correction* can be considered, provided there are no symptoms of hyponatraemia.
Severe	<120	Intravenous correction is usually needed: correction at 4 mmol/L over 24 hours with a maximum correction of 8 mmol/L for 24 hours. Regardless of neurological symptoms, an initial bolus of 3-5 mL/kg of 3% saline over 1 hour can be considered.

- Sodium deficit: Weight in kg x 0.6 x (140 - current serum sodium)
- If 0.9% NaCl is used:
  - The volume of 0.9% saline required to address the sodium deficit = Sodium deficit /0.154.
- If 3% NaCl is used:
  - The volume of 3% saline required to address the sodium deficit = Sodium deficit / 0.513
- Calculating the time (in hours) needed to correct the deficit: = 2 x (140 – current serum sodium)
- DO NOT CORRECT TOO FAST. Serum sodium should not increase >8 mmol/L in 24 hrs. Stop additional sodium replacement when it reaches 135 mmol/L

* The same calculations apply (for sodium deficit and the time to correct the deficit), whether for IVI or oral correction.

- Both generalised and focal seizures are common in children with TBM and can occur at any time in the disease course. The reasons for seizures in the acute phase include meningeal irritation, cerebral oedema with raised intracranial pressure, infarction, tuberculoma, and electrolyte disturbance, particularly hyponatraemia or hypoglycaemia. A significant number of survivors may develop epilepsy. Routine use of anti-convulsants in children with TBM is not currently recommended. Children with status epilepticus (SE) should be managed according to local SE guidelines. Children with recurrent seizures require anti-convulsant therapy with consideration of age and sex, available therapies, and drug-drug interactions. For example, carbamazepine should preferably be avoided while children are receiving rifampicin.
- Feeding interventions are indicated in children unable to feed due to a reduced level of consciousness or neurological deficit (e.g. pseudobulbar palsy). Appropriate orogastric or nasogastric feeding should be implemented, and placement of a percutaneous endoscopic gastrostomy (PEG) should be considered.

Criteria for discharge of CNS TB/TBM patients

The following criteria should be reviewed when considering discharge to home whilst on anti-tuberculosis therapy:

- Good tolerance of treatment.
- Caregivers who have good insight and demonstrated ability to administer and adhere to treatment.
- Social circumstances conducive to strict medication adherence, appointments, and access to transport in case of emergency.
- A named clinician who will take over the care of the patient post-discharge.
- Follow-up facilities that can detect missed appointments and have the ability to recall patients who do not arrive.
- The ability to re-admit the patient for investigation or observation if any concerns arise post-discharge.
- Although deafness is an unusual complication of TBM, a hearing test should be performed where possible. Vision assessment can be done as part of the full neurological assessment, with a referral for specialised assessment in selected patients.
- For children with neuro-disability, referral to occupational therapists, physiotherapists, speech therapists, etc., should be done as early as possible to preserve and improve function and to prevent contractures. The caregivers should be taught how to manage their child's neurological problems, optimise mobility and access resources, including mobility aids.
- Caregivers should be assisted in accessing the Care Dependency or Child Support grants.

10.5 Other forms of central nervous system TB

10.5.1 Tuberculoma

Anti-tuberculosis therapy is the same as for TBM. There are no data to guide the use of corticosteroids in the management of children with normal lumbar puncture and no neurological features; however, because the involvement of the brain and meninges cannot be excluded through lumbar puncture and/or imaging, and because deterioration on therapy is common in the first month after initiation of therapy, we recommend the use of prednisone in all children.

10.5.2 Spinal arachnoiditis

Tuberculous arachnoiditis can develop in the spinal cord in the absence of bone disease through the breakdown of granulomatous foci in the cord or meninges. If this is identified on an MRI, it should be managed as TBM. If there is uncertainty, it should be discussed with an expert or referred for assessment.

10.6 Miliary tuberculosis

Treatment should not be delayed while waiting for results; the anti-tuberculosis drug regimen is the same as for TBM. There are no data to guide the use of corticosteroids in the management of children with a normal LP and no neurological features; however, because the involvement of the brain and meninges cannot be excluded through LP and/or imaging, and because deterioration on therapy is common in the first month after initiation of therapy, the use of prednisone in all children with miliary tuberculosis is recommended.

11 Peri-natal TB

11.1 Definitions

Perinatal TB in infants < 3 months of age can be either congenital or postnatal in origin.

- **Congenital TB** is transmitted in utero through 1) transplacental spread through the umbilical vein to the fetal liver (in utero) or through 2) aspiration or ingestion of infected amniotic fluid (in utero/ intrapartum)
- **Postnatal TB** occurs through the inhalation of *M.tb* bacilli spread via the airborne route from a close contact (mother or other source patient) with infectious PTB soon after birth.

As it is difficult to distinguish congenital TB from postnatal TB, the term "**perinatal TB**" is preferred:

- **Perinatal TB** is defined as TB in infants within the first three months of life who were likely infected congenitally or within the first days of life postnatally.

11.2 Epidemiology

- Due to pregnancy-related immunological changes, women are at higher risk of developing TB disease during pregnancy and the immediate postpartum period.
- HIV infection further increases this risk, and the TB prevalence in pregnancy in HIV-positive women can be as high as 11% in high HIV-burden countries[14]
- TB in pregnancy is associated with poor pregnancy outcomes such as preterm birth, low birth weight infants, birth asphyxia and perinatal death.
- Undiagnosed and untreated TB during pregnancy and postpartum holds a high risk for perinatal TB infection and TB disease in infants.
- Due to immaturity of the immune system related to younger age, approximately 50% of babies infected with TB during the first year of life will develop TB disease in the absence of preventive measures. As many as 30% of these infants will develop severe disease. [15]

Perinatal TB in young infants is underdiagnosed and leads to severe morbidity and high mortality.

14 Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis. (2012) 55:1532–49. doi: 10.1093/cid/cis732

15 Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JR, et al. The natural history of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. (2004) 8:392–402.

11.3 Assessing a newborn for TB infection or TB disease

Many young infants with TB are the index (first diagnosed) patient. In most patients, the mother is found to be the TB source patient, but her diagnosis was missed during antenatal care!

- When mothers are diagnosed and/or treated for TB in pregnancy, their neonates should be assessed for **TB disease** at birth or within the 1st days of life. **TB preventive therapy** should be instituted if the infant is clinically well but exposed to TB, while prompt initiation of **TB treatment** is essential if TB disease is likely (See *Figure 12 on page 56*).

History of exposure

A newborn has had significant exposure to an infectious TB source patient if:

- The baby was born to a mother with TB and the mother:
  - was started on treatment for TB ≤ 2 months before delivery or
  - is demonstrating poor clinical response to TB treatment or
  - is TB smear or TB culture positive at delivery or
  - was diagnosed with TB soon after delivery

OR

- The baby has been exposed to a person (adult or adolescent) with pulmonary TB who shared the same enclosed space for one or more nights or for frequent or extended daytime periods (e.g. crèche or similar) during the three months before the index patient started appropriate TB treatment.

11.4 Clinical presentation of TB disease in neonates and young infants

- Infants with congenital TB may be symptomatic within the first days of life but typically become ill between 2 and 4 weeks of age. Some can be diagnosed as late as five months of age.
- Symptom onset in young infants is often acute over days rather than chronic over weeks as in older children and adults.
- The clinical picture may vary from asymptomatic or vague symptoms to severe acute or chronic illness.
- Congenital TB may differ in presentation from postnatal TB:
  - congenital TB patients more often present with acute respiratory distress, hepatomegaly, and/or abdominal signs.
  - postnatal TB often presents with cough, tachypnoea, and occasionally with wheeze or stridor.

Given the high risk of TB disease, the non-specific clinical presentation of TB in infants, and high morbidity and mortality, there should be a low threshold for rapid referral of unwell TB-exposed neonates and young infants with any (acute or chronic) symptoms or signs indicative of TB.

The most common symptoms and signs of perinatal TB are summarised in *Table 11 on page 53*.

Table 11 Symptoms and signs of perinatal TB

Frequency of occurrence	Symptoms and signs of TB in the neonate
Very common (i.e., > 60%)	• Respiratory distress, including tachypnoea • Hepatomegaly • Fever (usually low-grade)
Common (i.e., 40–60%)	• Cough may be acute or chronic (specifically >2 weeks of age) • Prematurity/low birth weight • Failure to thrive (growth failure) • Splenomegaly
Frequent (i.e., 25–40%)	• Poor feeding • Abdominal distension (including ascites)
Infrequent (i.e., 10–25%)	• Irritability and lethargy • Peripheral lymphadenopathy • Sepsis syndrome • Seizures
Rare (i.e., < 10%)	• Skin papular/pustular or ulcerative lesions, jaundice (obstructive), otorrhoea/mastoiditis, wheeze or stridor, apnoea or cyanosis attacks, vomiting, facial nerve palsy, shock, hemophagocytic lymphohistiocytosis
Source: Schaaf HS, Bekker A and Rabie H (2023) Perinatal tuberculosis—An approach to an under-recognized diagnosis. Front. Public Health 11:1239734. Doi: 10.3389/fpubh.2023.1239734	

11.5 Special investigations

Similar principles apply as detailed in *Section 6.4 on page 15*, with the following nuances applicable to neonates and very young infants:

- **Chest X-ray** remains a crucial tool for diagnosing perinatal TB. *Table 12 on page 54* summarises common chest X-ray features observed in perinatal TB.
- **Abdominal ultrasound** is important in presumed congenital TB; ultrasound can identify hypoechoic lesions in the liver and spleen, confirm ascites in infants with abdominal distension, and identify intra-abdominal or retroperitoneal lymphadenopathy.
- As with children of all ages, every effort should be made to obtain **bacteriological confirmation** and DST. The bacteriological confirmation rate in young infants can be as high as 70-80%, possibly due to uncontrolled multiplication of bacilli in the absence of a well-developed immune system. Repeated specimens may need to be tested to confirm the diagnosis. Asymptomatic children may yield positive bacteriological tests from gastric aspirates, possibly due to ingestion of amniotic fluid.
- There is currently no data on the use of TB-NAAT on stool specimens or U-LAM in perinatal TB.
- To confirm congenital TB, the **placenta could be examined** for granulomas.
- CXR and other relevant bacteriological specimens should be examined in the mother.

Table 12 Common Chest X-ray features in perinatal TB

Chest X-ray feature	Occurrence
Alveolar pneumonic opacification	30–40%
Miliary infiltrates	30–40%
Bilateral bronchopneumonic infiltrates	15–20%
Intrathoracic lymph nodes	10–15%
Pleural effusion	<5%
Cavities	<5%
Normal chest x-ray	5–10%

11.6 Treatment regimens for perinatal TB

The treatment principles of DS-TB in neonates are similar to those used in other children, although **infants < 3 months of age are not eligible for treatment shortening.**

Treatment consists of two phases:

- **An intensive phase** consisting of four drugs given for 2 months:
  - isoniazid, rifampicin and pyrazinamide, and
  - a fourth drug: either ethambutol or ethionamide
    - ethionamide can be considered in infants younger than three months or weighing < 3kg, given the challenges with ethambutol administration and monitoring for ocular toxicity in the very young.

- A **continuation phase** consisting of two drugs for four months, provided the child has an appropriate clinical response.
  - Isoniazid and rifampicin

- The duration of the continuation phase depends on the initial diagnosis and the response to therapy.
- TB drugs are dosed in weight bands and should be adjusted as the child grows.
- *Table 8 on page 42* provides detailed information on treatment duration and weight-banded drug dosages for children ≥ 2kg.
- If the infant weighs less than 2 kg, consult an expert.

11.7 TB preventive therapy in the exposed/infected neonate[16]

In neonates with TB exposure, TPT should be provided **once TB disease has been excluded**. The choice of TPT will depend on:

- the potential for drug interactions with ARVs taken either as treatment (DTG) or prophylaxis for HIV exposure (NVP) and
- the drug susceptibility test result of the source patient

For more information, please refer to the 2023 TPT guideline and the 2023 RR-TB Clinical Reference Guide. [17]

11.8 Separation of infants from their mothers for TB infection control

- Support the mother to adhere to her own TB treatment and the infant's TPT.
- It is not recommended that infants be separated from their mothers after birth, even if the mother is known to still be contagious.
- Establishing breastfeeding and bonding with the newborn infant is important.
- The mother should be advised on infection prevention and control measures, such as wearing a mask when handling or feeding the infant until she has been on effective therapy for at least two weeks and/or her sputum is smear-negative for acid-fast bacilli.
- Other measures include sleeping in a separate room if feasible and allowing ventilation in the home.
- Monthly follow-up of the infant to evaluate for TB disease is important.

11.9 Algorithm for the management of the TB exposed newborn

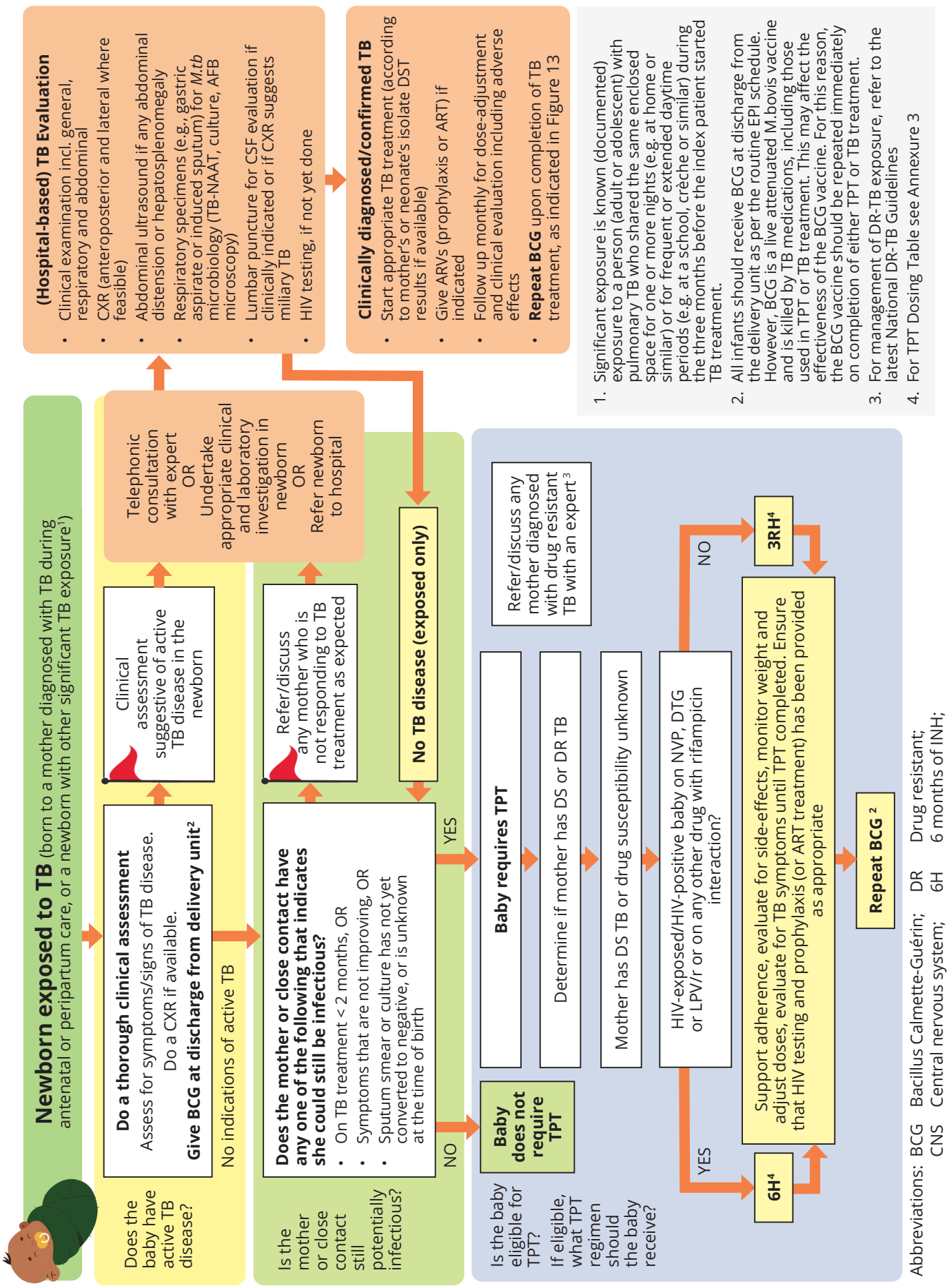


Figure 12 Management of the newborn exposed to TB

Considerations when deciding when to give the BCG vaccine.

- All healthy newborns should receive the BCG vaccine at discharge from the delivery unit, regardless of TB exposure or HIV exposure status.
- For infants that are transferred to a neonatal unit, the timing of BCG vaccination will depend on the infant's clinical status. Neonatal units should have a policy to ensure vaccination occurs prior to hospital discharge
- If the infant initiates TPT or TB treatment in the first six weeks[18] of life, the effectiveness of the live, attenuated BCG vaccine may be negatively impacted. Therefore, the BCG vaccine should be repeated on completion of either TPT or TB treatment. Infants or children living with HIV should be 1) on ART, 2) clinically well, and 3) have a CD4 > 25%.
- Infants living with HIV may have an additional CD4 count to determine if the infant meets the criteria for receiving BCG. Do not wait for the routine annual CD4 count to be done for ART monitoring purposes, as this delay may result in many infants not receiving BCG at all.
- Regardless of the service point at which the child is receiving either TPT or TB treatment, a comprehensive package of services should be provided as per the RTHB, including routine HIV testing for the HIV-exposed infant, immunisations, and growth monitoring.
- Any infant who tests positive for HIV at birth or at any time during TPT or TB treatment should be initiated on ART.
- The BCG vaccine can be administered at any vaccination visit, with other routine vaccines.
- It is acceptable to open a BCG vial for just one infant.
- Children with suspected or confirmed inborn errors of immunity or other acquired immunodeficiency conditions should be discussed with an expert before giving BCG
- A 'catch-up' BCG should be administered to any child <10 years of age who did not get a BCG at birth. Infants or children living with HIV should be 1) on ART, 2) clinically well, and 3) have a CD4 > 25% (if ≤5 years of age) or >200 cells (if >5 years of age).
- Pharmacovigilance and reporting serious adverse events (SAE) remain important for all age groups.

The recommendations for providing BCG are summarised in ***Figure 13*** below.

In delivery unit	**When to repeat BCG in infants who initiated TPT or TB treatment in the first 6 weeks of life**	
All newborns should receive BCG at discharge (regardless of HIV status or TB exposure status[1]) If living with HIV, initiate ART immediately	**Repeat BCG after completion of TPT or TB treatment [2]** If the infant is also LHIV, they should be on ART, clinically well, and have a CD4 > 25% [3] to be able to receive BCG**	** If the criteria to receive BCG are not met, i.e., the infant is - Not on ART, or - Unwell, or - CD4 < 25% → **Delay BCG until on ART and immunologically stable (CD4 > 25%)** → **Start/continue TPT until the child is eligible to receive BCG**

1. In the current data-free context, the recommendation to give all infants BCG at birth is based on operational considerations. The decision to give BCG or not and initiate TPT are often made by different people and sometimes in different facilities. When an intervention requires more than one service provider, more than one service location and multiple patient visits, the neonate may miss getting a BCG when indicated at birth, either because of a lapse in communication and continuity of care or because multiple visits become burdensome to the family.
2. **BCG vaccination should be done 24 hours after the last anti-TB treatment dose.** If the infant received rifapentine give BCG from 5 days after the last dose, and if the infant received bedaquiline or clofazamine give BCG vaccination two months after the last dose.
3. After TPT/TB treatment is completed, an additional CD4 count may be done to determine if the infant meets the criteria for receiving BCG.

Figure 13 When to give the BCG vaccine

18 Soares AP, Kwong Chung CKC, Choice T, Hughes EJ, Jacobs G, van Rensburg EJ, et al. Longitudinal Changes in CD4+ T-Cell Memory Responses Induced by BCG Vaccination of Newborns. The Journal of Infectious Diseases [Internet]. 2013 Jan 4;207(7):1084–94. Available from: http://dx.doi.org/10.1093/infdis/jis941

12 Treatment of children and adolescents with TB and HIV

Appropriate HIV care is essential to reduce the morbidity and mortality of children and adolescents living with HIV and TB. **Remember that:**

In a TB/HIV co-infected patient, TB cannot be treated without also treating HIV, and HIV cannot be treated without also treating TB!

Every child or adolescent being assessed for TB should have their HIV status determined and be managed appropriately.

12.1 Considerations for TB treatment

- Co-infected children are considered to have **advanced HIV disease.**
- Children living with HIV (CLHIV) on ART for more than three months and virologically suppressed **may be eligible for treatment shortening**, provided they have non-severe disease.
- All CALHIV and TB should receive vitamin B6 (pyridoxine) regardless of nutritional status.
- Clinicians should provide TB management as part of an **integrated care package** at clinical consultation visits. Failure to combine care leads to increased visit schedules and significantly increases the risk of disengagement and loss-to-follow-up (LTFU).

12.2 Considerations for antiretroviral treatment[19]

The timing of ART initiation

- In children newly diagnosed with HIV or children that disengaged from HIV care, ART should be started as soon as TB treatment is tolerated - ideally within two weeks after starting TB treatment unless there is TBM/CNS TB, in which case ART should be started after one month of TB treatment (refer to most recent ART Clinical Guidelines).

19 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. June 2023. Republic of South Africa National Department of Health. Available at: https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

Antiretroviral drug selection

DTG-containing regimens are preferred for all patients, including those on TB treatment. All ART naïve patients and patients re-initiating ART after previously interrupting ART should be initiated on a DTG-containing regimen. Patients on ART who have not yet been transitioned to a DTG-containing regimen should be evaluated and transitioned as a matter of urgency.

Patients who are not yet on ART when TB treatment is initiated:

- Initiate ART with a dolutegravir (DTG)-containing regimen, with DTG boosting, as explained in ***Table 13 on page 60*** below.

Patients who are already on ART when TB treatment is initiated:

- DTG-containing regimens:
  - Children and adolescents already on a DTG-containing regimen when TB treatment is initiated should continue the DTG-containing regimen whilst also taking TB treatment, with boosting of DTG as explained in ***Table 13 on page 60*** below.

- Efavirenz-containing regimens:
  - Most children and adolescents on ART should already have been switched to DTG-based regimens.
  - Adolescent patients who have not yet switched to a DTG-containing regimen but who are virally suppressed on an EFV-containing regimen when TB treatment is initiated should continue the EFV-containing regimen while also taking TB treatment. The EFV-containing regimen should be continued until two weeks after TB treatment is completed. After that, EFV can be switched to DTG.
  - If virally unsuppressed on EFV, switch to DTG immediately

- Protease Inhibitor (PI)-containing regimens:
  - All patients on a PI regimen should be transitioned to a DTG-containing regimen. The timing of the transition will be dependent on the VL, the time the patient has already been on the PI regimen, and the patient's level of adherence, as detailed on ***Page 15 of the 2023 ART Clinical Guideline***. PIs will only be used in an ART regimen if DTG is inactive based on a resistance test. However, during the transition process, some patients may still be on PI-containing regimens and may also require TB treatment. Rifampicin cannot be given with atazanavir (ATV/r) or darunavir (DRV/r). Significant drug interactions between lopinavir (LPV/r) and rifampicin should be managed as per ***Table 13 on page 60***

Prophylaxis of other opportunistic infections

- TB is a WHO Stage 3 defining illness. Co-trimoxazole should be initiated or restarted if previously discontinued, regardless of the CD4 count.

Management of drug-drug interactions

- Rifampicin-containing TB treatment has significant drug-drug interactions with all ART regimens.
- Rifampicin also has significant interactions with nevirapine (NVP) used as post-exposure prophylaxis to prevent vertical transmission in HIV-exposed infants.
- ART regimens should be adjusted as outlined in ***Table 13 on page 60*** below, with all dose adjustments continued until two weeks after the rifampicin is stopped.
- Additional drug interactions should be considered (for example, children on anticonvulsants or on other chronic medications that may interact with rifampicin – seek expert advice).

Table 13 Suggested dose adjustment for antiretroviral therapy in children and adolescents receiving rifampicin for TB treatment

Class	Drug	No adjustment needed	Do not use	Use with adjustment	Additional information
INSTI	**Dolutegravir**			X	**DTG-boosting** entails doubling the standard ("unboosted") dose by giving it twice daily rather than once daily. • For adolescents, the dosing frequency of DTG should be increased to 50 mg 12-hourly. If on TLD FDC, add 50 mg of DTG 12 hours after the TLD dose. • For DTG-boosting in children, please refer to the "Drug Dosing Chart" on ***page 34 of the 2023 ART Clinical Guideline***
	Raltegravir			X	Switching to dolutegravir is preferred.
	Cabotegravir		X		Do not use with rifampicin.
	Bictegravir		X		Do not use with rifampicin.
PI	**Lopinavir/ r**			X	**LPV/r tablets:** Double-dose lopinavir/r tablets in adolescents and children able to swallow whole LPV/r tablets **LPV/r solution or pellets or 4 in 1** (ABC/3TC/LPV/r): Super-boosting with additional ritonavir powder: maintain standard LPV/r dose but add additional ritonavir twice daily as per "Drug Dosing Chart" on ***page 34 of the 2023 ART Clinical Guideline***
	Atazanavir/r		X		Do not use with rifampicin.
	Darunavir/ r		X		Do not use with rifampicin.
NNRTI	**Efavirenz**	X			If virally suppressed on EFV when TB treatment is initiated, continue EFV until two weeks after completion of TB treatment. If virally unsuppressed on EFV, switch to DTG.
	Nevirapine (ART for a CLHIV)		X		Neonates < 3kg or < 4 weeks of age living with HIV on nevirapine-based ART should be discussed with an expert.
	Nevirapine (PEP for the HEI)		X		Breastfeeding infants on nevirapine-based VTP can stop NVP if mothers have achieved undetectable VL. If not, discuss with an expert.
	Rilpivirine		X		Do not use with rifampicin.
All NRTIs		X			No clinically significant interactions between rifampicin and ABC, TDF, TAF, AZT, 3TC or FTC

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; CLHIV, children living with HIV; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; HEI, HIV-exposed infant; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PEP, post-exposure prophylaxis; PI, protease inhibitor; r, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate, TLD, ART regimen containing tenofovir, lamivudine, dolutegravir; VTP, vertical transmission prevention; VL, viral load

VL monitoring and management

- In children and adolescents on ART and TB treatment, routine ART monitoring tests remain unchanged, as illustrated in *Table 14 on page 61*.
- Additional tests should be done if clinically indicated at the time of TB diagnosis and at any other time.

Table 14 Routine monitoring tests for children and adolescents on ART

Routine Monitoring test for clients on ART					Additional tests at TB diagnosis	Additional tests when clinically indicaed
	At ART start	At 3 months on ART	At 10-12 months on ART*	Annually at 12 monthly Intervals		
CD4 Count	X		X		X	X
Creatinine and eGFR (if on TDF)	X	X	X	X		
Viral Load		X	X	X	X	X
HBVsAg	X					X
* Aligned with 6-monthly scripting cycle						

12.3 Supporting adherence

Treatment adherence is crucial to treatment success. Providing appropriate adherence support begins with understanding the factors that could make adherence difficult for your patient. Use patient-centred communication to create a safe, nonjudgmental space for your patient to discuss challenges.

Treating TB and HIV at the same time can impact adherence because of:

- Increased pill burden
- Drug side effects or unpalatable medicines.
- Cost of clinic visits to the patient or family, e.g. transport, loss of income, cost of paying another person to take on social responsibilities, especially if care is not provided in an integrated and coordinated manner as described in *Section 13 on page 63*.

For those patients newly initiating ART:

Provide them with the knowledge and skills to adhere to ART and TB treatment using patient-centred communication, as outlined in *Section 13 on page 63*. See also the Differentiated Models of Care (DMOC) SOP 1 Fast track initiation Counselling for guidance.

For patients already on ART:

The development of a new opportunistic infection such as TB in a patient on ART should raise a 'red flag' for possible adherence problems and virological failure!

- Adherence to ART should be assessed by:
  - Doing a viral load: a suppressed VL is the most sensitive indicator of good adherence.
  - Asking open-ended questions, e.g. "What makes it difficult for you to collect or take your treatment?"
- If not suppressed:
  - The patient requires a thorough ABCDE assessment and management as detailed on *Pages 21-23 of the 2023 ART Clinical Guidelines*
  - A CD4 count must be done: If CD4 < 200, provide a package of care for Advanced HIV Disease
  - Provide enhanced adherence counselling (DMOC SOP 2) and Disclosure counselling (DMOC SOP 3), if indicated.

For all other aspects of HIV management, please refer to the most recent ART guidelines, currently the **'2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates'**.[20]

Remember that if a patient is already non-adherent on ART when TB treatment starts, they may struggle to adhere to ART and TB treatment! Carefully assess the root causes of non-adherence and tailor.

HELPLINE

If in doubt about any aspect of HIV or TB management, contact one of the following resources:

National HIV & TB Health Care Worker Hotline:
0800 212 506

Right to Care Paediatric Adolescent and Adult HIV Helpline:
082 352 6642

KZN Paediatric Hotline:
082 352 6642

20 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. June 2023. Republic of South Africa National Department of Health. Available at: https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents [accessed 7 Dec 2023].

13 Patient-centred care

Once TB is diagnosed, appropriate treatment can be initiated, and the episode can be managed as outlined in *Sections 8* onwards. However, the "What" of clinical management will be that much more effective if we also consider the "How," the "Who," and the "Where" these services should be delivered.

A patient-centred approach is a crucial component of the "How" of service delivery.

Patient-centred care is the practice of caring for patients (and their families) in ways that are meaningful and valuable to the individual patient. Patient-centred care is care that:

- **Listens** to and involves patients/caregivers in their care.
- **Respects** the patient/caregiver's values, preferences and expressed needs.
- **Provides information and education**, emotional support and alleviation of fear and anxiety.
- Coordinates and integrates care.
- Supports access to and **continuity of care** as well as transition of care if needed.

Two essential underlying mechanisms that enable patient-centered care are 1) effective communication and 2) providing care in a coordinated and integrated manner.

1. **Good communication** enhances the healthcare worker-patient relationship and improves adherence. Good patient education results in the following:

   - An informed patient/caregiver
   - An empowered patient/caregiver
   - A less fearful patient/caregiver
   - Better treatment outcomes

1. **Providing care in a coordinated and integrated manner** contributes greatly to a positive care experience. It reduces costs to the patient, reduces time away from work or other family care responsibilities, and is a crucial component of "How" services are delivered. This approach to care acknowledges that the TB episode being treated is only one component of the child's healthcare needs, and the child's health needs are only one component of the family's healthcare needs, as illustrated in *Figure 14 below.*

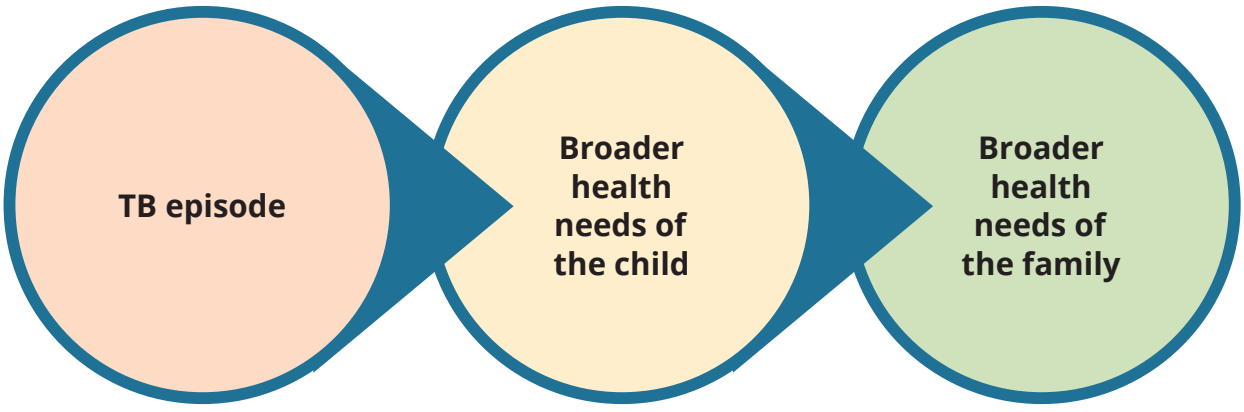


Figure 14 Treating a child for TB within a family context

Integration and coordination of care can be categorised as follows:

- **Level 1**: Provide an integrated and comprehensive package of all care required for the child in one consulting room.
- **Level 2**: As relevant, align the mother's TB treatment, family planning visits, PrEP or ART, and VL monitoring with the child's visit schedule, so the mother-child pair need only attend the single facility once for both consultations on the same day.
- **Level 3** (gold standard): Child and mother receive all needed care on the same day, in the same consultation room, by the same service provider.

Although Level 3 integration may not always be feasible for a child on TB treatment, primary care facilities should, at a minimum, provide Level 1 integration and strive to provide Level 2 integration wherever possible.

Providing integrated care and coordinating care for the child and their mother/ caregiver starts by understanding all the potential components of care that a mother/caregiver and child may need, as illustrated in *Figure 15.*

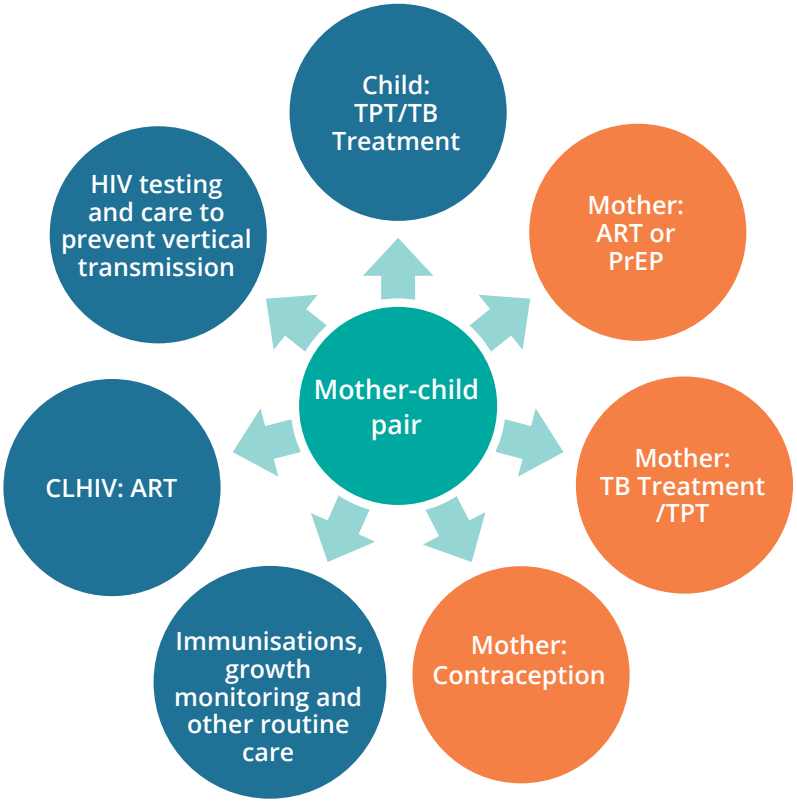


Figure 15 Components of care that may be required for a mother-child pair

A practical approach is as follows:

- Wherever possible, align the visit schedule for TB management and any other care the child may need **with the EPI visit schedule.**
- Aim to provide all care for the child at the same service point or at least **on the same return date** and **at the same facility.**
- Wherever possible, try to **align the mother's visit schedule** for ART, VL monitoring, and family planning with that of the child's visit schedule so the mother-child pair need only attend the facility once for both consultations on the same day.

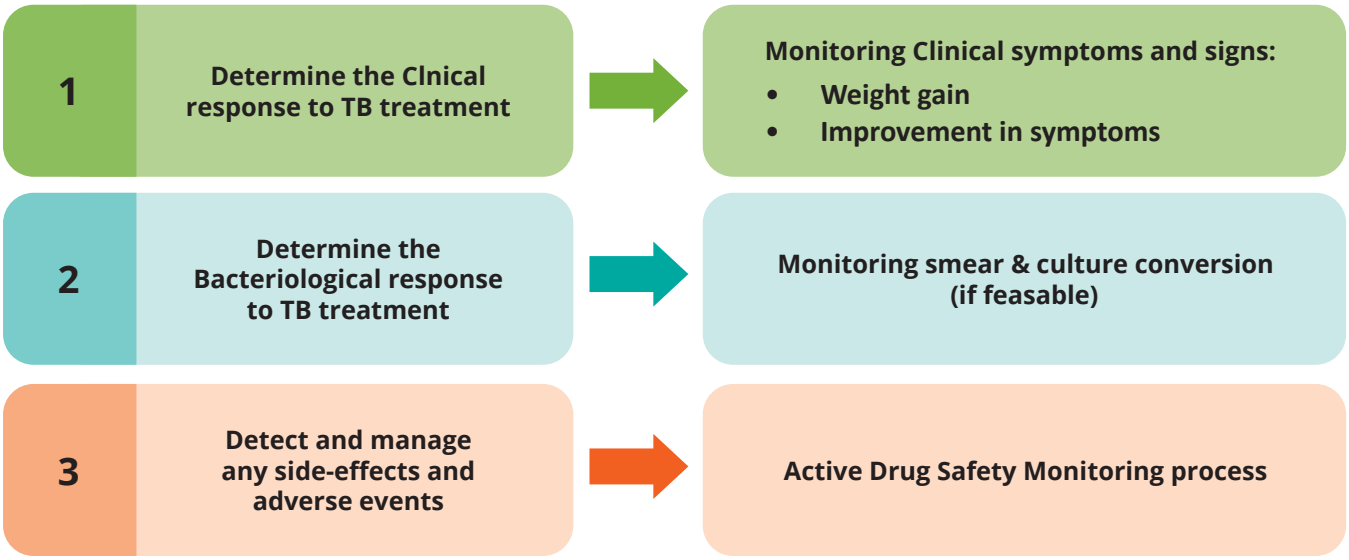
Clinicians should provide TB services as part of an integrated package of care at clinical consultation visits. Failure to integrate care leads to increased visit schedules and significantly increases the risk of disengagement and loss-to-follow-up (LTFU).

For the "Who" and "Where" of serviced delivery, please see *Annexure 1 on page 79.*

14 Monitoring and management of children and adolescents on TB treatment

Quality care at the follow-up visit is essential to promote adherence, minimise side effects and toxicities, and optimise clinical outcomes. Also, remember to integrate other care into follow-up visits, such as growth monitoring and immunisations, as discussed in *Section 13 on page 63*, Patient-Centred Care.

A patient on TB treatment should be monitored to:



14.1 Clinical monitoring

- Most children will respond well to TB treatment.
- **Children responding well to treatment will have a resolution of symptoms and will gain weight**.
- Children should be monitored at least monthly for the first two months and every two months until treatment is completed.
- The child/adolescent should be assessed at each visit for:
  - The presence (and change) of TB symptoms
  - Treatment adherence - review the patient treatment card (Green card) and conduct pill counts. At least 80% - ideally more – of all prescribed medication should be taken.
  - Any adverse events
  - Weight gain:
    - measure and record the patient's weight.
    - review medication dosages and adjust according to weight.
- The TB diagnosis, weight, and outcome of each follow-up visit should be recorded in the child's Road-to-Health booklet and the TB treatment card. If vaccinations are not up to date, catch-up vaccinations should be given.

Assessing treatment response after four months on the shortened treatment regimen

- **The response to treatment** will determine if the child is **eligible to end** the new shortened treatment regimen after four months of treatment.
- The final decision on treatment duration should be made during the follow-up visit at the end of month four.

- An adequate response for a patient with pulmonary TB:
  - Symptoms should have resolved or be significantly better, and documented weight gain should occur at one month of therapy.
  - After four months in therapy, the weight should show an appropriate and improving trend, and all symptoms should be resolved.
- An adequate response for a patient with cervical TB lymphadenitis:
  - There should be a reduction in lymph node size at four months of therapy.
  - If there was no significant reduction in the size of the lymph nodes, enlargement of nodes or complications, especially if TB was not bacteriologically confirmed, refer for further investigation (biopsy or aspiration) to exclude other diagnoses.
  - If the size is similar, the diagnosis is confirmed, and there are no additional concerns, therapy should be extended to 6 months.
- If there has been an **adequate clinical response**, treatment can be stopped after four completed months of TB treatment. The child would have received two months of intensive phase treatment and two months of continuation phase treatment.
- If there has been an **inadequate clinical response**, treatment can be extended beyond four months for a total of six months. The regimen will then consist of two months of intensive phase treatment and four months of continuation phase treatment.
- These children who do not have an adequate response to treatment should be evaluated for DR-TB and non-TB-related diseases (e.g., malignancy or HIV-related lung disease), as well as poor treatment adherence, as discussed in *Section 14.5 on page 70*.

14.2 The role of CXRs during TB management

- The CXR is a poor indicator of treatment response, as the intra-thoracic lymph nodes can initially enlarge because of the improvement in the child's immunity or due to ART in CLHIV. Therefore, follow-up CXRs are **not routinely recommended** in children with non-severe TB or asymptomatic children during or at the end of TB treatment.
- **Follow-up CXRs** should be performed if there is:
  - any clinical deterioration during TB treatment.
  - is no clinical improvement.
  - at the end of treatment for children with severe PTB, to assess for post-TB lung disease.

14.3 Bacteriological monitoring

- Confirming the result of the initial culture specimen at follow-up visits is very important.
- Bacteriological monitoring in children with a good clinical response is rarely implemented due to difficulties around sample collection.
- If, however, a child was smear or culture positive at TB diagnosis, treatment response can be monitored using smear microscopy/culture conversion, as done routinely in adults.
- If smear microscopy was negative at baseline in older children, smear microscopy should not be repeated unless there is clinical deterioration.
- NAAT testing should NOT be used to monitor response to treatment.
- Re-evaluating the bacteriological status of a child becomes a priority if there is clinical deterioration or if there is a new exposure to a source patient with DR-TB.

14.4 Management of adverse drug events

An adverse event (AE) is any untoward medical occurance that presents in a TB/ART patient during treatment with a pharmaceutical product.

It is important to prevent, recognise, and manage adverse events timeously because AEs can:

- **Affect adherence which lead to treatment failure**
- **Interfere with clients normal functioning and quality of life**
- **Cause permanent disability**
- **Be life threatening**
- **Result in death**

Inadequate management of side effects and adverse events is the main reason patients discontinue medications and, therefore, one of the primary reasons for treatment failure.

- Adverse events caused by TB medications are **less common** in children than in adults.
- The most important adverse event on first-line medication is **hepatotoxicity** (drug-induced liver injury), which can be caused by isoniazid, rifampicin, or pyrazinamide and, very rarely, by ethambutol.
- These are most likely to occur in the first eight weeks of treatment and are rare (5% or lower) in children.
- Serum liver enzyme levels should not be monitored routinely in children with DS-TB, as asymptomatic mild elevation of serum liver enzymes (<5 times normal values) is not an indication to stop treatment.
- **Optic neuritis** due to ethambutol (EMB) is rare if the dose remains below 25mg/kg/day. However, any complaint of visual disturbance should be taken seriously:
    - EMB should be stopped, and the child should be referred for ophthalmologic evaluation where possible.
    - Optic neuritis is reversible if EMB is stopped.

14.4.1 Management of drug-induced liver injury

The occurrence of new-onset jaundice, new onset/persistent nausea and/or vomiting, liver tenderness, hepatomegaly or abdominal pain should lead to urgent evaluation to determine the cause of these new symptoms – either drug-induced liver injury (hepatotoxicity) or another cause (e.g. hepatitis A).

Management of jaundice by a nurse at the PHC level

If a nurse detects jaundice in a child or adolescent on TB treatment, they should:

- Stop all anti-TB treatment immediately.
- Refer urgently (same day) for an assessment by a doctor.
- Do a finger-prick glucose while awaiting referral and manage according to the Integrated Management of Childhood Illnesses (IMCI) guidelines.
- If feasible, perform liver enzyme (alanine aminotransferase; ALT) and bilirubin (BR) tests while awaiting referral. However, referral is the priority and should not be delayed waiting for blood results.
- The following jaundiced patients should be referred directly for admission and assessment in hospital:
    - Children who are unable to hold down any food or drink (irrespective of whether they are dehydrated) or
    - Children or adolescents with any other clinical signs of liver failure (bleeding or any signs of confusion, altered level of consciousness or alterations in sleep-wake pattern).

Initial assessment of DILI where a doctor is available

- If clinical features of liver failure:
  - Do a clotting profile, full liver enzyme profile and finger-prick blood glucose.
- If not jaundiced and the patient can eat/drink:
  - Do liver enzyme (alanine aminotransferase; ALT) and bilirubin (BR) tests the same day and review the patient in 24 hours. Additional testing should be guided by the presumed diagnosis, including screening for viral hepatitis, especially Hep A.
- Children who present with other symptoms (not jaundiced and no signs of liver failure):
  - do ALT and BR and review within 24-48 hours.

Further management according to blood results

If ALT ≥ 100 IU/L OR total serum bilirubin ≥ 34 µmol/L in a symptomatic child:

THIS IS A LIVER INJURY THAT REQUIRES THE CESSATION OF DRUGS

- STOP TB treatment (and ART and other hepatotoxic drugs, e.g., co-trimoxazole, fluconazole, amoxicillin-clavulanic acid).
- Do full liver enzyme profile, INR and blood glucose.
- If INR ≥ 1.5, refer the child as presumed liver failure.
- If INR < 1.5 but ≥ 1.2, repeat in 48-72 hours and counsel the caregiver to return immediately if any signs of liver failure.
- If the repeat INR remains between 1.2 and 1.5, monitoring of the INR should be continued, and the child should be referred if the INR increases or does not normalise.
- Calculate ratio (R): ALT/upper limit of normal (ULN) divided by ALP/ULN, and interpret as per *Table 15 on page 68*.

Table 15 Interpreting the ALT: ALP ratio

Pattern of DILI	Interpretation of ALT: ALP ratio	Causative agents
Hepatocellular DILI	**ALT is disproportionately elevated compared to the elevation of ALP:** • ALT ≥ 3 times ULN with Ratio ≥ 5	• Isoniazid, pyrazinamide, nevirapine, efavirenz, acute viral hepatitis, chronic hepatitis B and C, • IRIS (immune reconstitution inflammatory syndrome)
Cholestatic DILI	**ALP is disproportionately elevated compared to ALT:** • ALP ≥ 2 times ULN with Ratio ≤ 2	• Rifampicin, amoxicillin-clavulanic acid, cephalosporins, sulfonylureas
ALP = serum alkaline phosphatase; ALT = serum alanine aminotransferase; ULN = upper limit of normal		

If ALT < 100 IU/L but > 40 IU/L AND total bilirubin < 34 µmol/L in a symptomatic child:

This is a potential DILI requiring close monitoring

- Continue TB treatment (if TB confirmed or presumed) and ART (if applicable).
- Monitor for jaundice and other symptoms or signs of drug-induced liver injury (DILI).
- Monitor every one to two weeks until normalised.
- If not normalised within 4-6 weeks, discuss with an expert so that other causes can be considered.

If ALT ≥ 200 in an asymptomatic child (for whom ALT was done for another reason)

This is a liver injury that requires the cessation of drugs

- see the protocol above.

If ALT > 100 IU/L but < 200 IU/L in an asymptomatic child (for whom ALT was done for another reason)

- Monitor weekly until normalised.
- If not normalised within 4-6 weeks, it must be discussed with an expert to consider other causes.

Managing a child with DILI that required cessation of TB drugs:

- No attempt should be made to reintroduce hepatotoxic drugs until bilirubin and liver enzymes have normalised (<2 x upper limit of normal (ULN)).
- An adjusted regimen with less hepatotoxic drugs (e.g., ethambutol, levofloxacin, terizidone, linezolid and/or amikacin) should be considered in **children with severe forms of TB such as TBM or miliary TB** until rechallenge of first-line treatment can occur (usually within <1 week). If the child has TBM, it is important to take into account the need for drugs that adequately penetrate the CSF.
- Once alanine ALT and BR levels have normalised (ALT and BR <2 times the upper limit of normal [ULN), rifampicin and isoniazid (and rarely pyrazinamide) can be rechallenged, as in most patients, hepatotoxicity will not recur.
    - Rifampicin (or isoniazid) should be rechallenged first at the required daily dose.
    - After 2-3 days, the ALT (and BR if previously abnormal) should be repeated.
    - If ALT remains <5 times ULN (or if < 3 times ULN in the presence of symptoms), add isoniazid (or rifampicin) at the full daily required dose and repeat the ALT after a further 2-3 days.
- If symptoms recur or ALT/BR increases to >5 times ULN, the drug responsible should be permanently stopped.
- If ALT/LFTs remain normal, stop other non-hepatotoxic anti-TB drugs (except in severe disease and within the first two months of treatment, continue ethambutol with/without levofloxacin).
- Pyrazinamide is often not rechallenged as it is the most likely cause of hepatotoxicity. If PZA has to be discontinued in the intensive phase, the duration of treatment may need to be extended up to 9 months in total.

14.5 Management of a child who deteriorates on treatment or has treatment failure

An **inadequate response** despite adequate treatment can be defined as:

- Clinical deterioration (experiencing a worsening of symptoms) or
- Not responding to treatment (persistent cough, poor weight gain) or
- A positive smear or culture at the end of the intensive phase
- If there was no initial bacteriological confirmation of disease, consider treatment failure when clinical symptoms are not improving or worsening, and/or if the CXR shows disease progression.

Possible causes to consider in children who are not improving on TB treatment are:

- Poor intake of TB drugs due to **side effects** such as vomiting, **non-adherence** to therapy, or **poor drug absorption.**
- Consider **drug resistance** in a child after excluding non-adherence to treatment, which may lead to drug resistance. Bacteriological testing and first-line DST should be conducted in such patients.
- If a child fails to respond to TB treatment within the first 1-2 months, and a clinical TB diagnosis was made without bacteriological confirmation, the healthcare worker must continue considering **alternative diagnoses** and refer the child for evaluation for alternative diagnosis and appropriate treatment.
- Sometimes, there may be slow clinical progress and delayed smear conversion due to **very severe pulmonary disease** with extensive cavitation and a high bacillary load.

Assess potential causes by asking the following questions:

- Is the child taking the drugs as prescribed (good adherence)?
- Are the drug dosages correct?
- Is it possible that the child or adolescent has poor gastrointestinal absorption of the medicine?
- Is the child or adolescent experiencing medication side effects or toxicity?
- Is the child or adolescent living with HIV (or any other reason for immune suppression)? If so, have they developed TB-IRIS or other opportunistic infections?
- Is the child or adolescent severely malnourished? And if yes, have they been managed appropriately?
- Is there a reason to consider DR-TB (source patient has DR-TB, is a re-treatment patient, is also not responding to therapy, or is not adherent to treatment)?
- Is there another reason for the child's illness other than, or in addition, to TB?
- Any child with persistent symptoms or who deteriorates on TB treatment should be referred to the next level of care for further assessment and management.

14.6 Managing TB treatment interruptions

- It is critically important to address the underlying reasons for treatment interruption.
- *Table 16 on page 71* describes the management of treatment interruption in children and adolescents receiving treatment for presumed or confirmed DS-TB.

Table 16 Management of treatment interruption in children and adolescents on first-line antituberculosis treatment

Treatment interruption details	Management
In all circumstances, if TB symptoms recur during the interruption, reassess the child or adolescent with a rapid molecular test and culture/DST to assess for drug resistance.	
Cumulative interruption < 1 month on a four or 6-month regimen	Add additional doses to the end of the relevant treatment phase.
Cumulative interruption > 1 month on the 4-month regimen	Change to 6-month treatment. If the interruption is in the intensive phase, add missed doses to the end of the intensive phase and continue for 6 months in total.
Cumulative interruption > 1 month on 6-month regimen	Add missed doses to the relevant treatment phase.
Interruption ≥ 2 months consecutively on the 4 or 6-month regimen	Assign outcome as 'loss to follow-up'. Repeat full clinical assessment of the patient (including radiology and bacteriological testing if available). Discuss with a clinician experienced in child and adolescent TB whether to restart a new treatment episode or monitor carefully for relapse. Factors to consider would be the clinical picture and overall adherence pattern. If unsure, restart a new treatment episode.

15 Recording and reporting of all children and adolescents with TB

Accurate and complete recording and reporting at every step of the TB care cascade is essential for effectively monitoring and evaluating TB control in children.

15.1 Basic concepts in monitoring & evaluation

	**Recording:** Process of capturing data or translating information to a specific format that is stored in a storage medium (e.g. paper or computer)
	**Reporting:** A formal account of proceedings or transactions (from one level to another) through reports, meetings, workshops, etc.
	**Monitoring:** Routine tracking of key elements of a programme through careful record-keeping and regular reporting (quarterly reporting, dashboard reporting, supervisory visits by subdistrict, district & province)
	**Evaluation:** Episodic, in-depth analysis of programme performance

15.2 Data collection tools

PHC Comprehensive Tick Register

A comprehensive data collection tool used to collect data elements for all health services rendered to patients. The PHC Tick register is used to collect TB screening data.

TB Identification (ID) Register (GW20/13)

TB Identification (ID) Register is used to record all children and adolescents who are eligible for TB test and/or TPT (e.g. screen positive for TB / contacts of TB index patients, newly diagnosed with HIV, etc.

Clinical stationery

Two **facility-held** standardised data collection tools are available to record the clinical information of children and adolescents who are initiated on TB treatment (either for TB disease or for TB infection):

1. The blue facility-held TB Treatment Record (GW 20/12)
2. The Ideal Clinic Patient Health Record

TB patient treatment card (GW20/15)

The green **patient-held** card records treatment details, including daily doses taken for individuals on TB treatment.

Tier.net Digital Surveillance System

This was formally known as the "TB Register" in its paper-based form. An electronic patient surveillance system that is used to collect TB and HIV information is used for the management of a child and adolescent on TB treatment.

District Health Information System (DHIS)

DHIS is used to monitor and report health programme performance. TB information related to children and adolescents must be captured and/or imported into DHIS.

15.3 Recording and reporting of children and adolescents with TB

Accurate and complete recording and reporting at every step of the TB care cascade is essential for effectively monitoring and evaluating TB control in children, as illustrated in *Figure 13 on page 57*.

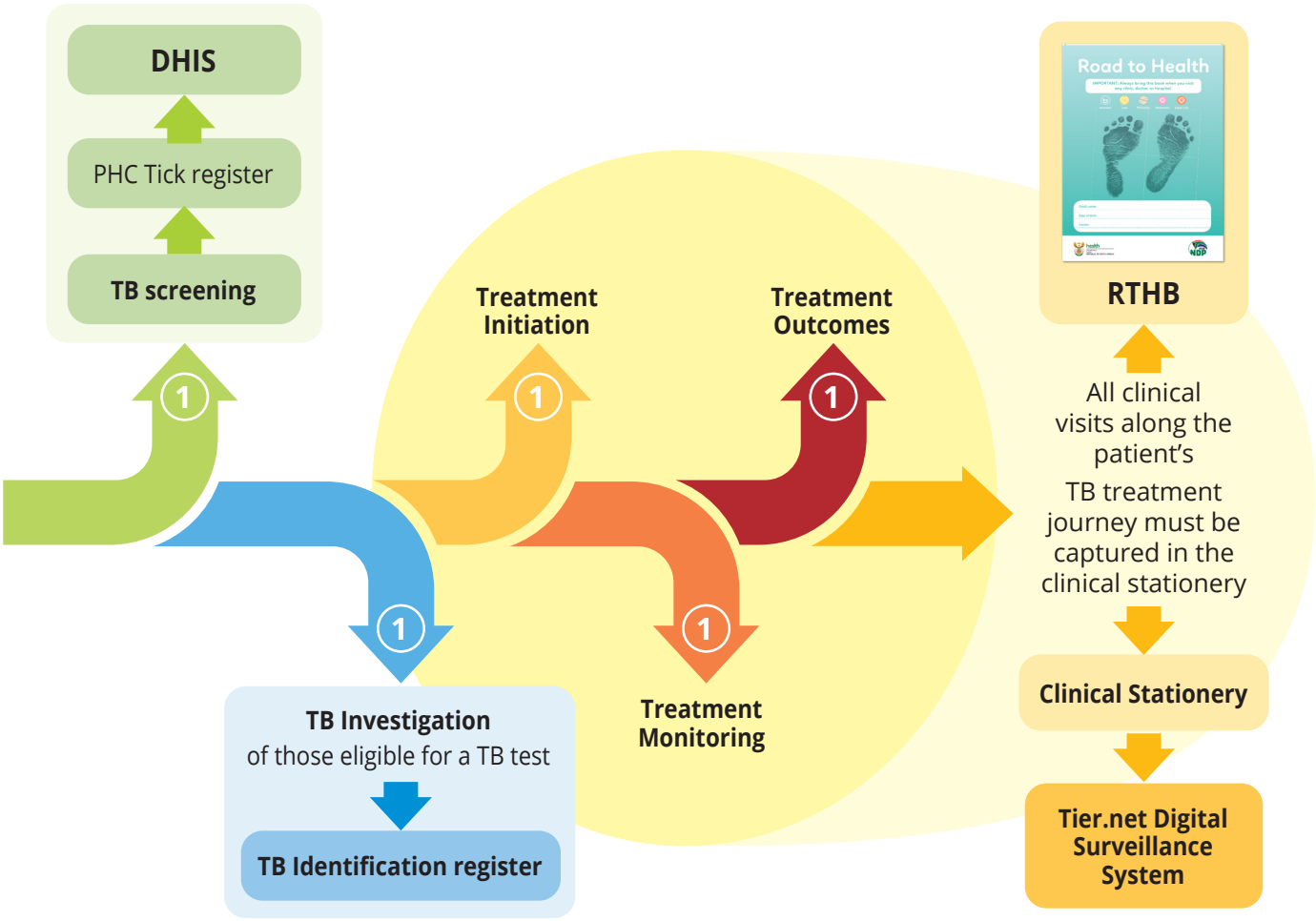


Figure 16 Tools for recording and reporting along the patient's journey

TB screening

- The IMCI guidelines and the TB screening tools must be followed to identify children and adolescents who are eligible for a TB test (TB investigations).
  - All children and adolescents must be screened for TB using the TB screening tool.
  - Children and adolescents screened should be recorded in the PHC tick register.
  - The screening data is captured into DHIS daily.

TB investigations

- All children and adolescents who are eligible for TB testing must be recorded in the TB Identification register (GW20/13).
- All investigations and outcomes must be recorded in the TB Identification register.
- The treatment start date must be recorded in the TB Identification register before opening a TB Treatment record.

Treatment initiation and monitoring

As soon as the diagnosis of TB is made, the following should occur:

- The clinical stationery (either the TB treatment record (GW20/12) or the Ideal Clinic Patient Health Record) must be completed, and the child must initiate treatment.
- The clinical stationery must be used to record all information pertaining to the following:
    - Treatment start date.
    - TB category and ICD 11 codes
    - Regimen provided.
    - HIV status and ART (if indicated)
- During each follow-up visit, the following should be recorded:
    - Visit dates.
    - Clinical notes, incl. weight, vital signs, changes in symptoms, and any side effects experienced.
    - Any tests conducted, and their results.
    - Any treatment dose adjustments.
    - Notes pertaining to adherence.
    - In addition to recording the information in the clinical stationery, the child's Road-to-health booklet must be updated.
- TB-related data from the clinical stationery must be captured in the Tier.net surveillance system after each visit and whenever clinically relevant data, such as culture results, become available.

TB Treatment outcomes

- At the end of the treatment, the treatment outcome must be recorded in the clinical stationery and the Tier.net Digital Surveillance System. Accurate recording at the facility level is important for properly evaluating the programme. The outcome definitions for children are as follows:

Outcome	Definition
Cured	A child who was respiratory specimen culture-positive pre-treatment and is respiratory specimen culture-negative in the last month of treatment and on at least one previous occasion, at least 30 days prior.
Completed treatment	A child who has completed treatment but does not meet the criteria to be classified as cured or treatment failure. Treatment response in a child with sputum smear or culture-negative TB or extrapulmonary TB is assessed monthly by monitoring the weight of the child and symptom resolution.
Treatment Success	The sum of treatment cured and completed.
Lost to Follow-Up	A child with treatment interrupted for ≥ 2 consecutive months for any reason without medical approval.
Died	A child who dies for any reason during TB treatment.
Treatment failure	A child who is sputum smear or culture-positive at five months or later after starting treatment.
Transferred out	A child who has been transferred to another district and for whom the treatment outcome is not known.

15.4 Data flow

Information is collected at the facility level using the PHC Tick register, TB Identification Register, the clinical stationery and Tier.net.

- At the end of the month, a TB Identification register summary sheet must be completed and be captured into DHIS.
- TB-related data from the clinical stationery must be captured in the Tier.net surveillance system after every visit and whenever clinically relevant data, such as culture results, becomes available.
- At the end of each quarter, data management principles for ensuring data quality must be followed before an export is created. All facilities must submit their exported data report to the next level of reporting for importing into DHIS.
- Standard reports must be analysed as required monthly, quarterly, and annually.
- On a monthly and quarterly basis, a set of data elements and indicators must be reported to enable programme monitoring. These data elements and indicators are as follows:

Table 17 Data elements for TB case finding and treatment initiation and their role in quality improvement at facility level

	Data Element Name	Definition	Use and Context	Tools / Source	Comment to Facility Manager
TB case finding and treatment initiation	PHC headcount under 5 years	All individual patients not yet reached five years (60 months) seen for PHC services at a facility	Monitors PHC access and utilisation for children under 5 years.	Daily Reception Headcount register or HPRS	Compare to PHC headcount under 5 to ensure that all children attending the facility are being screened for TB
	Screen for TB under 5 years	Children under 5 years who were screened in health facilities for TB using the standard TB screening tool	Identifies children under 5 years who should be triaged for TB testing or other investigations.	PHC Comprehensive Tick Register	
	Child under 5yrs eligible for TB test	Children under 5yrs who were eligible for TB testing based on a positive symptom screen using the TB symptom screening tool	Monitors efforts towards the early identification of TB in children under 5yrs.	TB Identification register	Bacteriological confirmation is always preferred but seldom done, especially at PHC levels. Up-referring children for diagnostic tests elsewhere incurs additional costs to the family and can result in disengagement from care. Comparing these two data elements will indicate if diagnostic samples are indeed being collected at your facility.
	TB test under 5 years using TB-NAAT	TB symptomatic and asymptomatic patient under 5 years who was tested using TB-NAAT	To monitor the number of children who had access to bacteriological testing compared to those who were eligible for a TB test	TB Identification register	
	DS-TB Bacteriologically confirmed under 5 years	Children under 5 years who were bacteriologically confirmed with TB-NAAT, or culture and DST as Rifampicin-Susceptible TB (RS-TB)	Monitors trends in early identification of patients with DS-TB in health care facilities.	TB Identification register	The sum of the two data elements, 'DS-TB clinically diagnosed' and 'DS-TB bacteriologically confirmed', provides the total of all children diagnosed with TB. Compare this total to the number of children started on treatment. The numbers diagnosed and started on treatment should be the same. If not, investigate the reason why children are diagnosed but not initiated on treatment
	DS-TB clinically diagnosed under 5 years	TB patient under 5 years who have been diagnosed based on clinical assessment and or non-bacteriological investigation	Every effort should be made to get bacteriological confirmation of disease, but the diagnosis can be made clinically.	TB Identification register	
	DS-TB treatment start under 5 years	Child under 5 years who were started on DS-TB treatment	This is a measure of linkage to treatment when compared to the total number diagnosed with TB (bacteriologically + clinically diagnosed)	TB Identification register	

Table 18 Data elements for identification and management of child contacts and their role in quality improvement at facility level

Identification and management of child contacts	DS-TB treatment start 5 years and older	Patients 5 years and older who were started on DS-TB treatment	Compare this to how many contacts under 5 have been identified relative to the number of "adults" started on treatment	TB Identification register	Children get TB from infectious adults and adolescents. Identifying child contacts and providing TPT is crucial in preventing TB in children. Compare the number of child contacts identified to the number of patients over 5 diagnosed with TB. Although not every TB patient over 5 will have contact with a younger child, many households do have young children. Although exact proportions cannot be estimated, it should raise a red flag if NO or very few children are identified as contacts when significant numbers of persons > 5 years are being diagnosed with TB. If resources allow, link all households with TB to a CHW. CHWs can assist with identification of child contacts, treatment support and re-engagement in care if needed. The *Contact line list tool* can facilitate this process.
	TB contact under 5 years	A TB contact is defined as a patient who has been in close contact with TB patient.	Identifies patients that need to be triaged for testing and eligibility for TPT	TB Identification register	
	TB contact under 5 years start on TPT	TB contact under 5 years who was started on TB Preventive Treatment (TPT).	Monitors TPT coverage amongst TB contacts	TB Identification register	

15.5 Operational considerations

When a child moves between different levels of care (e.g., diagnosis at a hospital but referred for treatment initiation/ continuation at a primary healthcare (PHC) facility, communication should be very clear between the levels of care to ensure that TB treatment is continued, and that the child is recorded in Tier.net

Creating strong linkages between general child health services and TB services remains essential, especially in facilities where services are physically separated. This is critical to enhance the quality of services and to ensure recording and reporting accuracy. See also Section 13,

16 Assessing post-TB health

TB can have **significant negative, longer-term effects** on a child's health and development, even after successfully completing TB treatment. For example:

- Pulmonary TB can result in reduced lung function, stunting and increased risk of developing TB again.
- TBM can have debilitating neurological sequelae resulting in physical and mental disabilities.
- TB of bones and joints may result in deformity and physical disability.

Therefore, each child or adolescent on TB treatment should be assigned a treatment outcome at the end of treatment, but follow-up **"special care"** (as per RTHB) may be needed beyond the conclusion of TB treatment.[21] The aim should be to provide **home-based care** and involve caregivers in rehabilitation as much as possible. As relevant, post-TB care should include:

- An assessment of their health-related quality of life and referral to an auxiliary worker as indicated, e.g., a physiotherapist, occupational therapist, and/or speech therapist.
- A nutritional assessment with referral to a nutritionist or dietician as needed.
- A **family-centred care approach** to promote the health and well-being of children, adolescents, and their families. Refer to a social worker if needed.

The WHO operational handbook on TB (Module 5: Management of Tuberculosis in Children and Adolescents), ***section 5.4, p. 131***, provides a detailed summary of current best practices based mostly on expert opinion.[22] Guidance will be updated as new evidence becomes available.

21 Definitions and reporting framework for tuberculosis: 2013 revision (updated December 2014 and January 2020). Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/79199,).

22 WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Annexure 1: Considerations for different levels of care

Services provided / Health system element to be present	PHC	CHC	District hospital	Regional/ tertiary hospital
Clear clinical and operational protocols for nurses in managing TB in children and adolescents	√	√	√	√
Provide TB screening services and TB clinical assessments for eligible persons.	√	√	√	√
Basic diagnostic sputum sample collection on children able to cough and expectorate	√	√	√	√
Nurse-initiated TB treatment as per IMCI protocols and management of uncomplicated TB	√	√	√	√
TB infection control practices in place	√	√	√	√
Provide HIV Testing services, initiate ART and maintain viral suppression.	√	√	√	√
Provide growth monitoring, nutritional screening and basic nutritional support.	√	√	√	√
Have access to a doctor for clinical advice and clear referral criteria and pathways to higher levels of care.	√	√	√	√
Clinical assessment by a doctor		√	√	√
More advanced sample collection, including gastric aspirates, sputum induction, NPA, FNAs		√	√	√
Availability of CXR and CXR interpretation by a doctor		√	√	√
Admission of ill and malnourished children			√	√
More invasive sample collection, including lumbar puncture, pleural or ascitic taps			√	√
Availability of imaging, e.g. ultrasound			√	√
Nutritional rehabilitation for severe malnutrition and/or severe anaemia			√	√
Referral criteria for accepting children with severe disease				√
Neuroimaging facilities				√
ICU and high-care facility for severely ill patients				√
Specialists able to manage pulmonary and extrapulmonary TB with severe features				√
A multi-disciplinary team including specialist paediatrician/physician, specialist neonatologist, physiotherapist, occupational therapists, social workers				√

Annexure 2: TB Screening Tool

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

TB SYMPTOMS SCREENING TOOL FOR ADULTS AND CHILDREN

PATIENT DETAILS

Surname: _____ **First Name:** _____

Physical Address: _____ **Age:** _____

_____

Cell Phone number: _____ **Patient Folder:** _____

MEDICAL HISTORY

	Tick the appropriate answer (√)		
Close contact of a person with infectious TB	Yes	No	Unknown
Type of Index Case	DS-TB	Rif Resistant TB	MDR/XDR TB
Uncontrolled Diabetic	Yes	No	
HIV Status	Positive	Negative	Unknown
Mine worker/Ex-mine worker			
Other (Specify)			

TB SYMPTOMS

1.ADULTS

Symptoms (Tick √)	**Yes**	**No**
Current cough of any duration		
Persistent fever for 2 weeks or more		
Unexplained weight loss of >1.5kg in a month, or failure to gain weight in pregnant women		
Drenching night sweats		

2. CHILDREN

Symptoms (Tick √)	**Yes**	**No**
Current cough of any duration		
Persistent fever for 2 weeks or more		
Fatigue/less playful		
Weight loss or failure to thrive.		

If "yes" to one or more of these questions, consider TB

If the patient is coughing, collect sputum specimen and send it for TB-NAAT

If the patient is not coughing but has other symptoms, clinically assess the patient, or refer for further investigation.

Date of the last TB test: _____

Annexure 3: TPT Dosing Chart

TPT REGIMENS FOR CHILDREN WEIGHING LESS THAN 25 KILOGRAMS

There are two potential regimens for children: 3RH (rifampicin and isoniazid for 3 months), and 6H (isoniazid for 6 months). The choice depends on the child's weight, HIV status or HIV exposure (maternal HIV) status:

- in HIV-negative children < 25kg, the priority regimen is 3RH
- in children living with HIV and on DTG (dolutegravir) containing ART, the preferred regimen is 6H to avoid drug-drug interactions with ART
- in infants born to HIV-positive women (HIV-exposed but HIV-negative infants) on nevirapine, 6H is the priority regimen as rifampicin lowers nevirapine levels below efficacy

All children and breastfeeding infants require pyridoxine (vitamin B6) for the duration of their TPT as follows: Children younger than five years 12.5 mg and children five years or older 25 mg, once daily. Lack of pyridoxine access should not be a barrier to receiving TPT.

For HIV-positive infants who have just had the Bacillus Calmette-Guérin (BCG) vaccine and are not TB-exposed, TPT should be deferred for 14 weeks as Isoniazid (INH) impairs the effect of live BCG (*M.bovis* BCG) vaccine.

1. RECOMMENDED DAILY DOSAGES FOR 3RH IN HIV-NEGATIVE CHILDREN <25KG

Child's Weight (kg)	RH (Daily) fixed dose combinations		Duration
	75 / 50	If dispersed in water	
2 - 2.9	½ tablet	5ml	3 months
3 - 3.9	¾ tablet	7.5ml	
4 - 5.9	1 tablet	10ml	
6 - 7.9	1 ½ tablet	15ml	
8 - 11.9	2 tablets	20ml	
12 - 15.9	3 tablets	30ml	
16 - 24.9	4 tablets	40ml	
≥ 25	**Use adult formulations and doses**		

2. RECOMMENDED DAILY DOSAGES FOR 6H AMONGST CHILDREN LIVING WITH HIV < 25KG

Weight band (kg)	Daily INH 100mg tablet	Duration
2 - 3.4	¼ tablet	6 months
3.5 - 4.9	½ tablet	
5 - 7.4	¾ tablet	
7.5 - 9.9	1 tablet	
10 - 14.9	1½ tablet	
15 - 19.9	2 tablets	
20 - 24.9	3 tablets (or one 300mg tablet)	
≥ 25	**Use adult formulations (maximum dose 300 mg per day)**	

Annexure 4: New evidence and WHO recommendations on treatment for drug-susceptible (DS) TB

Young children, especially those <5 years of age, have a high risk of developing TB and severe forms of TB following exposure to Mycobacterium tuberculosis.9 Most children (>75%) with TB develop pulmonary disease, with most having non-severe forms of pulmonary TB (PTB).[23, 24] The most common form of extrapulmonary disease is peripheral TB lymphadenitis, which is also the only form of extrapulmonary TB disease that is classified as non-severe TB. Paediatric TB treatment recommendations in the past have generally extrapolated proven efficacy data from trials conducted in adults, who typically have more severe TB disease with high bacillary burden. Treatment-shortening trials in adults with non-severe forms of TB showed promising results.[25] It is, therefore, likely that most non-severe forms of TB disease in children, who typically have paucibacillary disease, can be treated with shorter treatment regimens. Evidence to support this was recently generated in the SHINE[26] trial of treatment shortening in children with non-severe TB.

SHINE[11] was a multi-centre, phase 3 open-label treatment-shortening non-inferiority trial in children with non-severe, symptomatic, smear-negative presumed drug-susceptible (DS)-TB. The study was conducted in South Africa, Uganda, Zambia and India. Children aged <16 years were randomised to 16- versus 24-week standard first-line anti-tuberculosis treatment using WHO-recommended paediatric fixed-dose combination (FDC) formulations. [11] Children were included in SHINE if they had non-severe TB on chest x-ray (CXR) and/or peripheral lymph node disease. They were microscopy smear-negative for acid-fast bacilli (AFB) on respiratory samples. Therefore, the collection of respiratory samples and CXR was required to assess TB disease severity in the trial.

All children received standard doses of rifampicin (RIF), isoniazid (INH) and pyrazinamide (PZA) as an FDC and ethambutol (EMB) was added to the regimen if this was standard practise according to National Guidelines at the site. Of the 1,145 children enrolled in SHINE and included in the final analysis, the majority, 716 (63%), received EMB in addition to the FDC, and 113 (10%) were living with HIV.

In conclusion, SHINE[11] showed that four months of TB treatment using standard first-line drugs was not inferior to the standard six-month treatment for children with non-severe TB. There was no difference between the six-month and four-month groups regarding the proportion with an unfavourable outcome (including deaths) or in the number of children with adverse effects. The standard dispersible FDC formulations were well-tolerated and were acceptable for children and their caregivers.[27] Based on these results, the WHO recommended in March 2022 that four months of TB treatment may be used as an alternative to the standard 6-month regimen in children aged between 3 months and 16 years with non-severe (presumed DS) TB.

The SHINE trial was not powered to provide evidence on treatment shortening in sub-groups, such as children and adolescents living with HIV (CALHIV). The sub-group analysis showed some evidence that the 4-month regimen was non-inferior to the 6-month regimen; however, only a small proportion of children with severe immunosuppression were included in this sub-group analysis. Thus, the WHO recommends that CALHIV with non-severe TB should be carefully monitored, especially at four months of TB treatment. If there is evidence of residual TB disease or poor treatment response, the duration of TB treatment should be extended to at least six months.

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23 Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. Int J Tuberc Lung Dis. 2006;10(7):732-8. PubMed PMID: 16848333

24 Wiseman CA, Gie RP, Starke JR, Schaaf HS, Donald PR, Cotton MF, Hesseling AC. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J. 2012;31(4):347-52. doi: 10.1097/INF.0b013e318243e27b. PubMed PMID: 22315002.

25 Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, Hermann D, Wallis RS, Johnson JL, Lienhardt C, Savic RM. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. Nat Med. 2018;24(11):1708-15. doi: 10.1038/s41591-018-0224-2. PubMed PMID: 30397355; PMCID: PMC6685538.

26 Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, Hissar S, Choo L, Musoke P, Mulenga V, Mave V, Joseph B, LeBeau K, Thomason MJ, Mboizi RB, Kapasa M, van der Zalm MM, Raichur P, Bhavani PK, McIlleron H, Demers AM, Aarnoutse R, Love-Koh J, Seddon JA, Welch SB, Graham SM, Hesseling AC, Gibb DM, Crook AM, Team ST. Shorter treatment for non-severe tuberculosis in African and Indian children. N Engl J Med. 2022;386(10):911-22. doi: 10.1056/NEJMoa2104535. PubMed PMID: 35263517; PMCID: PMC7612496.

27 Wademan DT, Busakwe L, Nicholson TJ, van der Zalm M, Palmer M, Workman J, Turkova A, Crook AM, Thomason MJ, Gibb DM, Seeley J, Hesseling A, Hoddinott G. Acceptability of a first-line anti-tuberculosis formulation for children: qualitative data from the SHINE trial. Int J Tuberc Lung Dis. 2019;23(12):1263-8. doi: 10.5588/ijtld.19.0115. PubMed PMID: 31931909; PMCID: PMC6903808.

Similarly, the SHINE trial was not powered to provide evidence on the efficacy of treatment shortening in the sub-group of children who did not receive ethambutol as the fourth drug in the intensive phase of treatment. The SHINE trial, therefore, provides evidence that children and adolescents with non-severe DS-TB can be safely treated for four months, with most of these children and adolescents receiving two months of intensive phase with four drugs (INH, RIF, PZA and EMB).

The WHO recommends the addition of EMB to the intensive phase of treatment in children and adolescents in settings with a high HIV prevalence and/or a high INH resistance prevalence. High HIV prevalence settings are defined as HIV prevalence ≥1% among adult pregnant women or ≥5% among people with TB. Thresholds for low, moderate or high levels of INH resistance prevalence are established by country National TB Programmes (NTPs).

In South Africa, the HIV prevalence amongst pregnant women was estimated at 30.0% (95% CI: 29.4%– 30.6%) in the 2019 National Antenatal Sentinel HIV Survey.[28] HIV prevalence amongst people with TB was 53% in 2021.1 There is limited recent data on the prevalence of INH mono-resistant TB in South Africa. A national study on the prevalence of drug-resistant (DR)-TB in South Africa from 2012 to 2014 (n=101,422) estimated INH mono-resistant TB prevalence to be higher than 5% in all nine provinces.[29] Another study conducted during the same period (2011-2014) in one of the high TB burden provinces, including nearly 90,000 drug susceptibility test (DST) results, found INH mono-resistance ranging from 13.8% to 21.1%.[30]

Given 1) the high HIV prevalence in South Africa, 2) the likely high prevalence of INH resistance, 3) the high proportion of children on the SHINE trial who received EMB and 4) the need for a simplified and standard approach to TB treatment, the decision was made to include EMB as a fourth drug in the intensive phase of TB treatment to all children and adolescents. This decision on EMB also means that all children and adolescents treated for DS-TB, whether for severe or non-severe TB, will receive the same drug regimen but with varying duration of the continuation phase, which simplifies implementation. Guidance on implementing treatment shortening, including assessing disease severity and eligibility for treatment shortening, is addressed in ***Section 8 on page 31***.

28 Woldesenbet SA, Lombard C, Manda S, Kufa T, Ayalew K, Cheyip M, Puren A. The 2019 National Antenatal Sentinel HIV Survey, South Africa, National Department of Health. 2021.

29 Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, Molebatsi T, van der Walt M, Adelekan A, Deyde V, Ihekweazu C, Madhi SA. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779-87. doi: 10.1016/S1473-3099(18)30222-6. PubMed PMID: 29685458; PMCID: PMC6800151.

30 Mvelase NR, Balakrishna Y, Lutchminarain K, Mlisana K. Evolving rifampicin and isoniazid mono-resistance in a high multidrug-resistant and extensively drug-resistant tuberculosis region: a retrospective data analysis. BMJ Open. 2019;9(11):e031663. doi: 10.1136/bmjopen-2019-031663. PubMed PMID: 31699736; PMCID: PMC6858147.

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