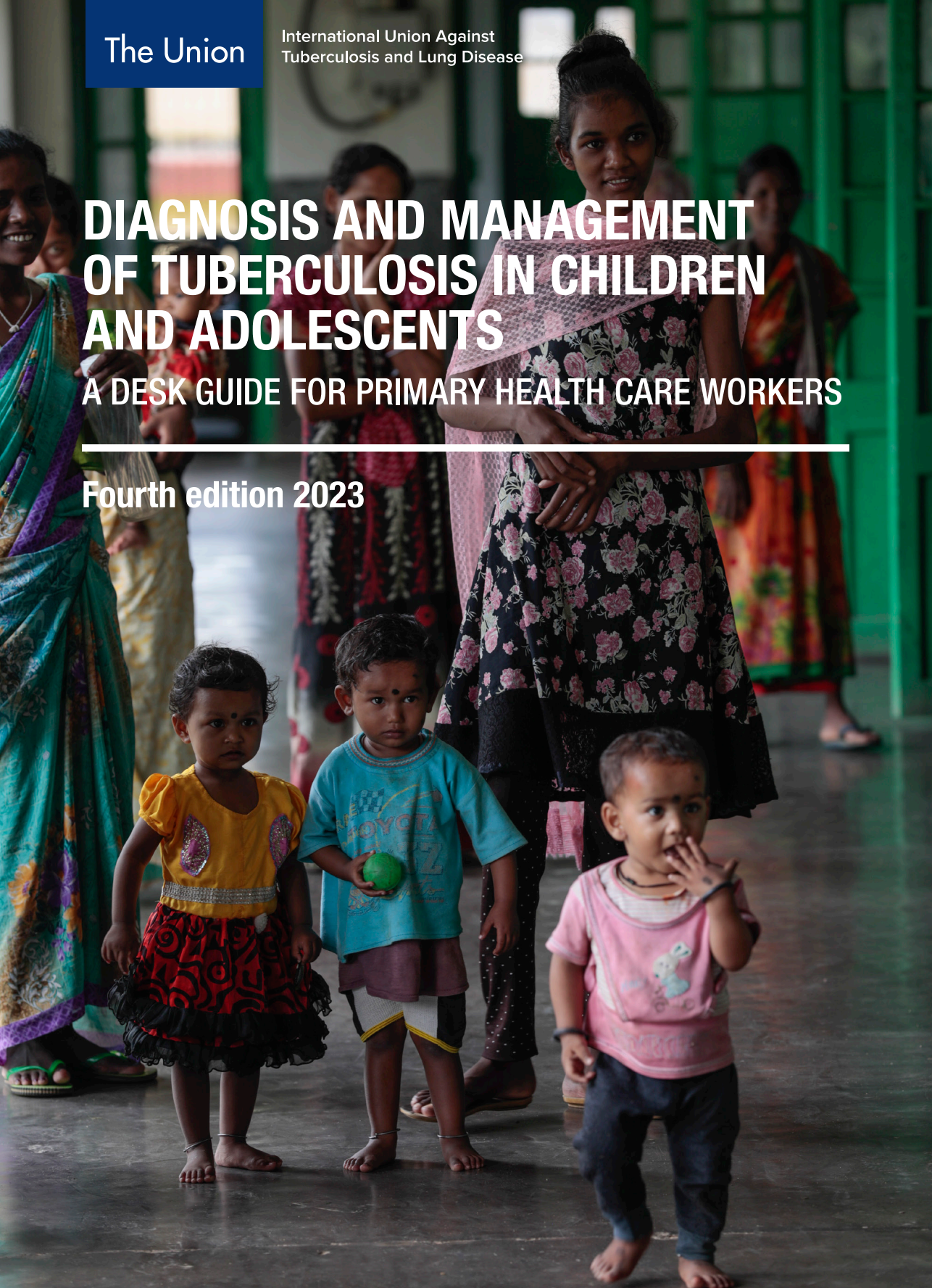


DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

A DESK GUIDE FOR PRIMARY HEALTH CARE WORKERS

Fourth edition 2023



DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

A DESK GUIDE FOR PRIMARY HEALTH CARE WORKERS

**Fourth edition
2023**

Stephen M. Graham and Jacquie N. Oliwa

© International Union Against Tuberculosis and Lung Disease (The Union)
2 Rue Jean Lantier, 75001 Paris, France

Fourth edition, 2023

Copyright is retained by The Union. Individuals wishing to reproduce material from the Guide must request written permission from publications@theunion.org. Likewise, authors who wish to include material from other copyrighted sources must seek permission from the copyright holders and provide written copy of this permission at the time of submitting their work.

The development of this publication was supported by a Cooperative Agreement NU2GGH002222 from the U.S. Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not represent the official views of the U.S. Centers for Disease Control and Prevention, the U.S. Department of Health and Human Services, or the U.S. Government.

ISBN: 979-10-91287-33-3

This desk Guide provides management Guidelines that are consistent with the World Health Organization's Consolidated Guidelines for child and adolescent tuberculosis published in 2022 and The Union's Management of Tuberculosis: A Guide to Essential Practice published in 2019. This desk Guide is a decision-aid intended for use by primary health care workers and does not cover all possible situations and/or solutions related to the management of childhood TB.

The clinical judgment of the health worker remains the basis for final decision-making, and this aid is not a substitute for clinical expertise and individual assessment. It aims to provide guidance for the more common and straightforward cases presenting for care in resource-limited settings.

Contents

Authorship and Acknowledgements	8
Abbreviations	9
Introduction	10
Epidemiology of tuberculosis in children	11
Clinical diagnosis	12
Pulmonary tuberculosis (PTB)	12
Clinical management of children and adolescents with presumptive tuberculosis	17
A management decision algorithm	18
Investigations	19
Bacteriological confirmation	19
Chest X-ray (CXR)	20
Testing for TB infection	25
HIV testing	25
Limitations of tuberculosis diagnostics in children	26
Extra-pulmonary tuberculosis (EPTB)	29
Management of tuberculosis: assessing disease severity	31
Tuberculosis treatment: some general rules	34
Additional management decisions	35

Follow-up and monitoring of tuberculosis in children and adolescents	36
Treatment interruption	37
Poor treatment response	38
Contact screening and management	39
Tuberculosis preventive treatment	40
Challenges for preventive therapy	41
Drug-resistant tuberculosis in children	42
Children and adolescents living with HIV	43
Tuberculosis diagnosis in children and adolescents living with HIV	43
Tuberculosis management in children and adolescents living with HIV	44
Management of babies born to women with tuberculosis	45
BCG vaccination	45
National tuberculosis programme management issues	46
Infection prevention and control	47
Definitions and distinctions	48
Resource materials	49
Appendix 1: Indications requiring hospitalisation for inpatient care and/or for further investigations	50
Appendix 2: Scores for clinical features with or without CXR findings	51
Appendix 3: Classification of severity on CXR	52
Appendix 4: Guidance for the screening and management of contacts	53

Authorship

International Union Against Tuberculosis and Lung Disease (The Union), Paris, France and Centre for International Child Health, University of Melbourne, Melbourne, Australia (*Stephen M. Graham*)

Kemri-Wellcome Trust Research Programme, Nairobi, Kenya and The University of Nairobi, Faculty of Health Sciences, Department of Paediatrics and Child Health, Nairobi, Kenya (*Jacquie N. Oliva*)

Acknowledgements

The Union recognises with gratitude the valuable contributions and feedback by the following: F Amanullah (Pakistan), C Chabala (Zambia), RA Dlodlo (The Union, Zimbabwe), JP Dongo (The Union, Uganda), KG Koura (The Union, France), S Maloney (USA), MP Sekadde (Uganda), J Tonsing (India) and R Triasih (Indonesia)

The CXR images presented are from The Union's Diagnostic CXR Atlas for Tuberculosis in Children: A Guide to Chest X-Ray Interpretation (2nd edition, 2022) and is freely available [here](#).

Abbreviations

AFB	Acid-fast bacilli
ART	Antiretroviral therapy
BCG	bacille Calmette-Guérin
CLHIV	Children living with HIV
CPT	Cotrimoxazole preventive therapy
CSF	Cerebrospinal fluid
CXR	Chest X-ray (radiograph)
DR-TB	Drug-resistant tuberculosis
EMB, E	Ethambutol
ETH, ETO, ETA	Ethionamide
EPTB	Extra-pulmonary tuberculosis
FDC	Fixed-dose combination
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
IPT	Isoniazid preventive therapy
INH, H	Isoniazid
LF-LAM	Lateral flow-lipoarabinomannan
mWRD	Molecular WHO-recommended rapid diagnostic test
MDR	Multidrug-resistant
MDR/RR	Multidrug/rifampicin-resistant
NTP	National tuberculosis programme
PLHIV	People living with HIV
PTB	Pulmonary tuberculosis
PZA, P	Pyrazinamide
RDT	Rapid diagnostic test
RIF, R	Rifampicin
RPT, P	Rifapentine
TB	Tuberculosis
TBM	Tuberculous meningitis
TST	Tuberculin skin test
TPT	Tuberculosis preventive treatment

Introduction

Tuberculosis (TB) is an important cause of illness and death in children and adolescents, especially in high TB incidence countries.

Around one and a half million children and adolescents become ill with TB every year, and nearly 250,000 children die from this curable and preventable disease.

Many TB cases in children and adolescents are not detected, especially in young children (<5 years), who account for most deaths in children due to TB.

Based on careful clinical assessment, the diagnosis of TB can be made in most children and adolescents in an outpatient setting.

Contact history is an important part of the assessment for diagnosis and prevention.

Every child and adolescent with presumptive or confirmed TB should be tested for HIV infection.

Children and adolescents with TB respond well to treatment.

All children with TB should be routinely registered with and reported to the national tuberculosis programme (NTP) of the country in question.

The desk Guide is primarily intended for:

1. Health workers who manage sick children and adolescents in primary-level health facilities or outpatient settings at any level of care, especially in high TB burden settings; and
2. NTP staff who manage children and adolescents as part of NTP work.

The desk Guide aims to improve:

1. Early and accurate case detection and diagnosis;
2. Timeliness of management and treatment outcomes; and
3. Appropriate child contact screening and management.

The desk Guide will focus on:

1. How to diagnose common forms of TB in children and adolescents;
2. To treat children and adolescents with TB;
3. When to refer children with TB; and
4. How to manage close contacts of people with TB.

Epidemiology of tuberculosis in children

TB in children and adolescents is common in high TB incidence countries. An estimated 1.5 million children and adolescents become ill with TB every year.

Pulmonary TB (PTB) is the most common form of child TB; it is often not bacteriologically confirmed.

Extra-pulmonary TB (EPTB) is also common and may coexist with pulmonary TB; presentation varies with age.

It is important to always consider age, recent TB contact(s), nutritional and HIV status, and risk factors for:

- TB infection: history of TB contact, whether residing in a high-incidence community.
- TB disease: young age, HIV infection/exposure, severe malnutrition, recent history of measles, recent contact with a TB patient.

TB is especially common after infection in young children (<5 years of age)

- The younger the child, the more likely it is to identify a close household contact with TB disease.
- TB disease can be more severe and of rapid onset in infants and young children.

Children with TB disease usually have poor weight gain and may lose weight or be malnourished.

The presentation and approach to diagnosis of PTB in adolescents (10–19 years) is similar to that for adults.

Any child or adolescent with presumed or confirmed TB should also be tested for HIV.

TB diagnosis and management can be more challenging in children and adolescents living with HIV.

The BCG vaccine is not fully protective against TB disease in children but is especially protective against severe forms of TB in infants and young children.

**TUBERCULOSIS CAN BE DIAGNOSED WITH CONFIDENCE IN THE MAJORITY OF CHILDREN
USING CAREFUL RECORDING OF PATIENT HISTORY AND CLINICAL ASSESSMENT**

Clinical diagnosis

Diagnosing TB in children and adolescents relies on a combination of a careful recording of patient history, including any account of recent TB contact or previous TB treatment and symptoms and signs consistent with TB. The following investigations are recommended:

- Clinical examination, including growth assessment
- HIV testing if status is unknown
- Bacteriological testing (if available)
- CXR (if 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.

Trial treatment with TB medicines is NOT recommended as a method of diagnosing TB in children.

Pulmonary tuberculosis (PTB)

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.

Common clinical presentations of PTB are persistent cough and/or poor weight gain. In most cases, children with TB develop unremitting symptoms that persist for more than 2 weeks without sustained improvement or resolution following treatment for differential diagnoses (e.g., antibiotics for pneumonia, anti-malarials for fever, nutritional rehabilitation for failure to thrive or malnutrition).

Note that in high-risk groups, such as infants or children living with HIV (CLHIV) or severely malnourished children, PTB can also present as acute pneumonia.

The approach to diagnosis of TB in CLHIV is similar to that for non-HIV-infected children. Health workers should have an increased degree of clinical suspicion of TB.

Typical symptoms of TB:

- Cough, especially if it is persistent and fails to improve
- Weight loss or failure to gain weight
- Prolonged fever and/or night sweats
- Fatigue, reduced playfulness, lower activity levels

There should be high index of suspicion, especially if symptoms persist (>2–3 weeks) without improvement following other appropriate therapies (e.g., antibiotics for cough anti-malarial treatment for fever; or nutritional rehabilitation for malnutrition).

History of contact:

- Close contact with a person with TB at home
- Contact may be with a person with TB from outside the household (e.g., carer, grandparent, relative) with whom the child has had frequent contact
- In older children and adolescents, contact with a source case is often outside the household, such as at school or in the neighbourhood
- A source case with bacteriologically confirmed PTB is more likely to infect contacts than cases with bacteriologically negative PTB
- Treatment regimen and treatment response of the source case should be determined
- If no source case is identified, any contact with a person with chronic cough should always be investigated; that person should be assessed for possible TB
- Timing of contact: children usually develop TB within 12 months following exposure; most (90%) develop TB within 6 months.

ALWAYS CHECK CONTACT HISTORY AND WEIGHT, RECORD WEIGHT AND COMPARE AGAINST PREVIOUS WEIGHTS IN THE ROAD-TO-HEALTH CARD/BOOKLET

Importance of follow-up assessments:

- Most children and adolescents with probable TB present as outpatients and do not have features of severe illness (e.g., respiratory distress, severe malnutrition) that require hospitalisation
 - Therefore, it is not always necessary to establish a diagnosis upon initial presentation. If not severely ill and in case of uncertainty about diagnosis and persistence of symptoms, a follow-up evaluation in 2–4 weeks should be arranged to reassess weight and persistence of or improvement in symptoms
 - This decision will be influenced by other factors, such as likelihood of the child to return for reassessment (such as living proximity, availability of transport). The child should be encouraged to return earlier if there is any deterioration of the symptoms.
-

Clinical examination:

- Poor weight gain: child should be weighed accurately, and the weights recorded in a weight-for-age curve in the child's health/road-to-health card/booklet; weight should be compared to previous weights in the past 3 months as recorded in this card/booklet
 - Signs of poor weight gain, weight loss or severe malnutrition should be checked
 - Evidence of faltering growth (static weight/flattening of growth curve, mid-upper arm circumference <11.5 cm) if earlier weights available should be checked
 - Vital signs
 - Fever and increased respiratory rate for age should be evaluated
 - Respiratory system
 - May have signs of respiratory distress, e.g., fast breathing, chest indrawing, head nodding, grunting
 - Auscultation and percussion are usually normal but may reveal lung disease (e.g., crackles, bronchial breathing, fixed area of wheezing due to airway narrowing from enlarged lymph nodes) or pleural effusion (dullness, reduced breath sounds)
 - Other physical signs suggestive of TB include:
 - Signs of extra-pulmonary TB, such as neck swelling or distended abdomen
 - Severe malnutrition, especially if not responding to therapeutic nutritional treatment
 - Acute pneumonia not responding to adequate course of antibiotics
 - Persistent wheeze not responding to bronchodilators.
-

Atypical clinical presentations of PTB:

- Acute pneumonia (especially in children <2 years of age or CLHIV)
 - May present with signs of severe or non-severe pneumonia
 - PTB should be suspected in case of poor response to antibiotics, especially with positive TB contact history
- Wheeze
 - Asymmetrical and persistent wheeze can be caused by airway compression due to enlarged tuberculous hilar lymph nodes
 - PTB should be suspected when wheeze is asymmetrical, persistent, not responsive to bronchodilator therapy and associated with other typical features of TB*

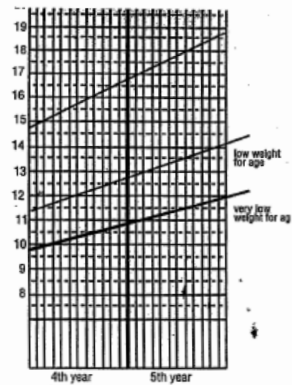
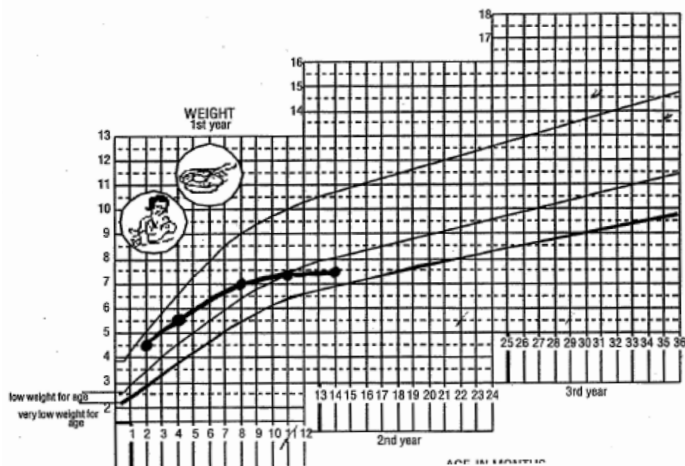
*Note that wheeze due to asthma is responsive to inhaled bronchodilator, usually recurrent and variable rather than persistent and is not associated with other typical features of TB, such as poor weight gain and persistent fever.

It is always important to check the child's weight, record it and compare with previous weights. Poor weight gain can be defined in any of the following ways:

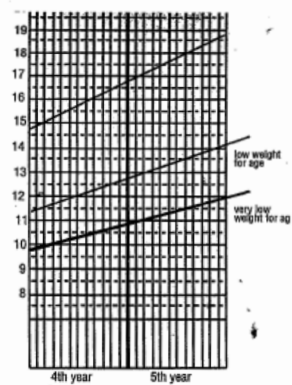
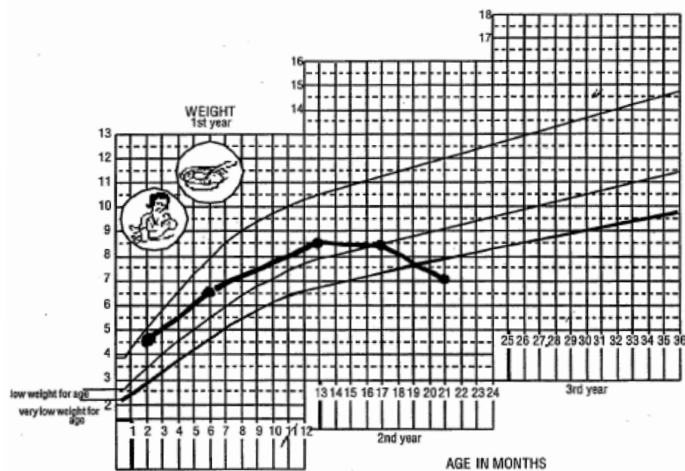
- Reported noticeable weight loss
- Very low weight or underweight
- Confirmed weight loss since last visit
- Flattening of growth curve.

The trajectory in the past 3 months is the most important indicator.

Growth faltering or “failure to thrive”



Weight loss (recent) and being underweight



Clinical management of children and adolescents with presumptive tuberculosis

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

The following important considerations need to be taken into account in any assessment of a child or adolescent with presumptive TB:

- Triage assessment: does the child or adolescent require immediate hospitalisation for inpatient care based on 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 HIV-infected?
- Does the child have risk factors for TB and for severe TB, such as being <2 years of age, HIV-infected or severely malnourished?
- Is it feasible to collect and send sample(s) for rapid diagnostic testing?
- Is CXR readily available and if 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?

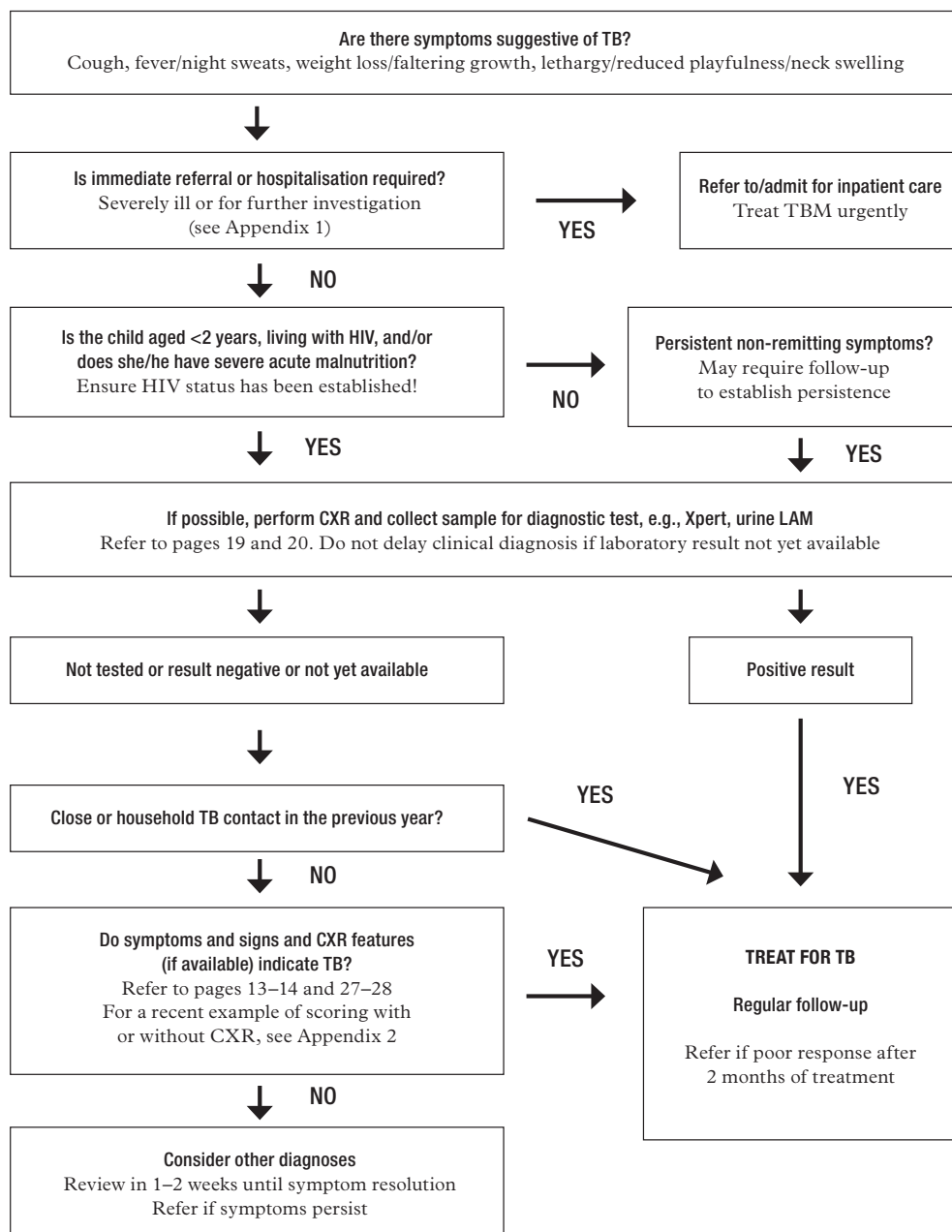
Treatment decisions also require specific considerations of:

- whether treatment initiation is urgent, such as in the case of TB meningitis (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
- whether the child or adolescent requires treatment for DR-TB
- whether there are comorbidities, such as HIV infection, severe malnutrition or severe anaemia, that require specific treatment.

The process from screening for presumptive TB to diagnosis and management of a child (<10 years) is outlined in the next section.

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.

A management decision algorithm



If the child does not fit definite criteria for TB treatment, decision for further review as outpatient or referral for additional opinion/investigation will depend upon the child's clinical condition and available levels of care.

Investigations

Bacteriological confirmation

Every effort should be made to establish bacteriological confirmation of TB and drug susceptibility, especially in young children.

Bacteriological confirmation is easier to establish in adolescents, who often have adult-type disease.

Bacteriological confirmation with testing for drug resistance is especially important for children and adolescents:

- Who may have drug-resistant TB, such as when the known contact has MDR/RR-TB or has had previous TB treatment
- Who are living with HIV
- Who have complicated or severe TB disease.

A range of sputum and other samples can be collected to seek bacteriological confirmation for PTB:

Expectorated sputum

- Usually children older than 10 years (sometimes as young as 5 years) can produce sputum by expectoration
- Risk of aerosolised transmission

Induced sputum (± nasopharyngeal aspiration)

- Requires electricity, hypertonic saline, suction and trained personnel
- Younger children may require additional nasopharyngeal aspiration after induction
- Risk of aerosolised transmission

Gastric aspirate

- Usually performed in younger children unable to provide sputum by expectoration
- Requires fasting before aspiration of swallowed sputum and overnight nasogastric tube placement

Nasopharyngeal aspirate

- Requires suction machine and specimen trap
- More suitable than induced sputum in case of respiratory distress

Stool

- Swallowed sputum containing TB bacilli from the lungs can pass through the gut and be detected using rapid molecular assays in stool samples.

Two samples provide a higher yield than one sample only.

Other specimens may be considered as appropriate for EPTB (Table 1, page 28); however, note that yield from bacteriological confirmation is variable:

- High for lymph node aspirate
- Moderate for cerebrospinal fluid
- Very low for pleural, pericardial or peritoneal aspirates.

Additional diagnostic tests for bacteriological confirmation and/or drug susceptibility which may be in use at secondary- or tertiary-level facilities include the following:

- Urine lateral flow-lipoarabinomannan (LF-LAM) assay
- Truenat® MTB and GenoType® MTBDRplus
- TB loop-mediated isothermal amplification (TB-LAMP)
- Line-probe assay (LPA)
- Culture and phenotypic or genotypic drug susceptibility testing.

Chest X-ray (CXR)

CXR is an important tool for the diagnosis of PTB in children who are bacteriologically negative or who cannot produce sputum.

CXR is also important in determining severity of pulmonary disease in order to make treatment decisions for shorter 4-month regimens in case of non-severe TB.

CXR is also very useful to identify forms of EPTB, such as miliary TB, pleural TB and pericardial TB (Table 1, page 28; see page 30 for examples).

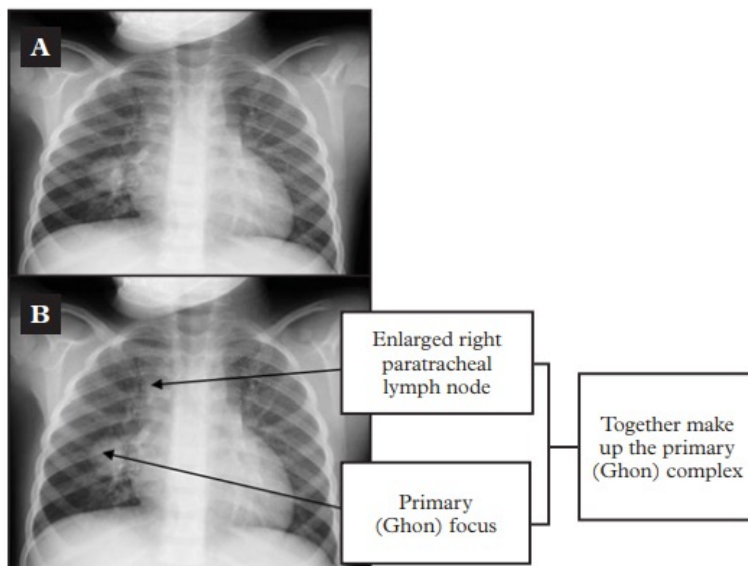
The following TB-related abnormalities may be visible on CXR:

- Enlarged hilar lymph nodes
- Narrowing or compression of large airways
- Opacification in lung tissue
- Miliary mottling in lung tissue
- Cavitation (tends to occur in older children)
- Pleural effusion
- Pericardial effusion
- Abnormality of thoracic vertebra

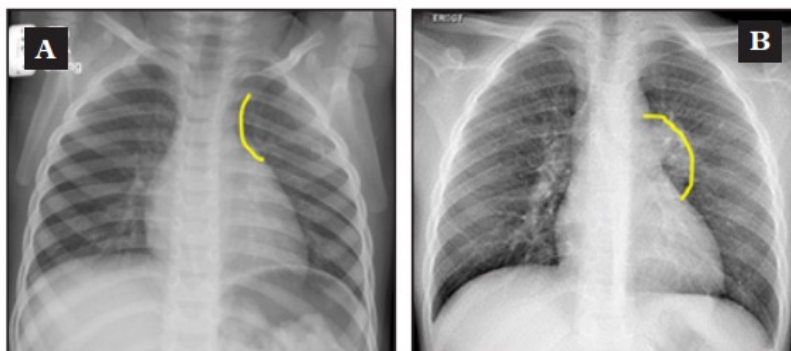
Abnormalities are shown using graphs in Appendix 3. A finding of marked abnormality on CXR in a child with no signs of respiratory distress (absence of rapid breathing or chest indrawing) is supportive of TB as a cause.

CXR features are also essential for distinguishing mild from severe PTB in children, as the NTP may propose differing treatment durations for the two groups (Table 2, page 32). Examples of common CXR abnormalities graded by severity are shown below (pages 21–24).

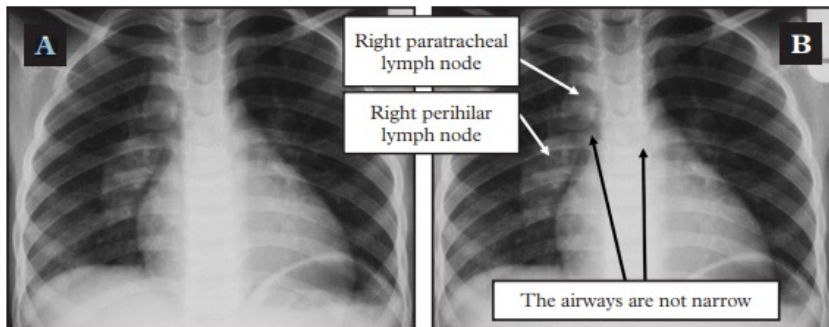
CXR features suggestive of TB in children



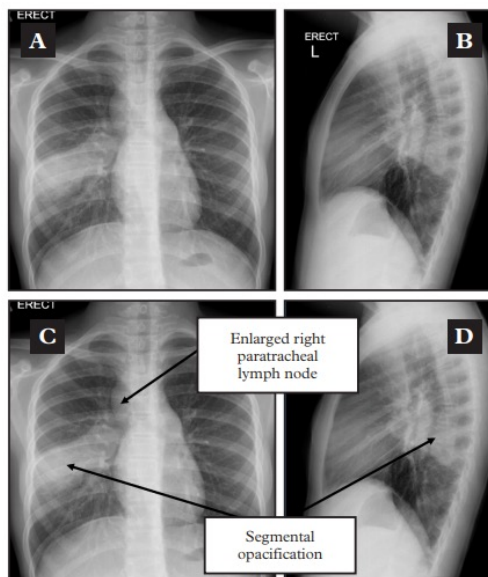
CXR (B) is an annotated version of CXR (A). This CXR shows a primary (Ghon) complex.



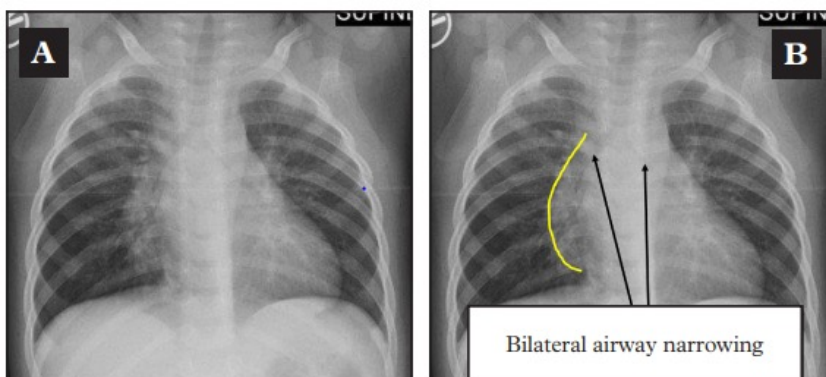
CXR (A) is normal; note that the hilar region has an inward convex shape.
 CXR (B) is abnormal with loss of clear curve due to an enlarged left perihilar lymph node.
 This indicates radiologically **non-severe** disease.



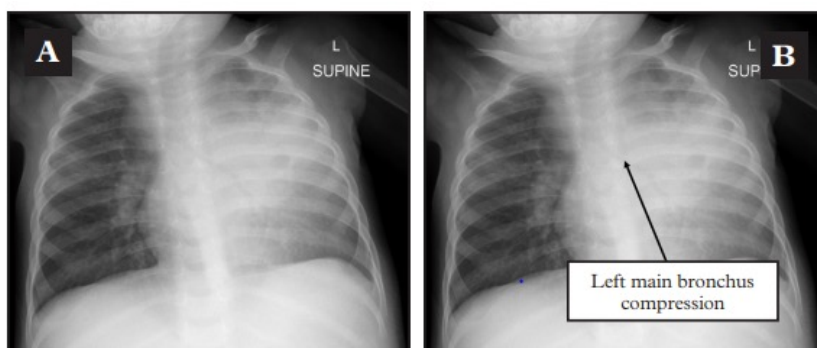
CXR (B) is an annotated version of CXR (A), which was taken from a 3-year-old child. This CXR shows enlarged paratracheal and perihilar lymph nodes on the right, with no airway or parenchymal involvement. This indicates radiologically **non-severe** disease. CXR (B) is abnormal with loss of clear curve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



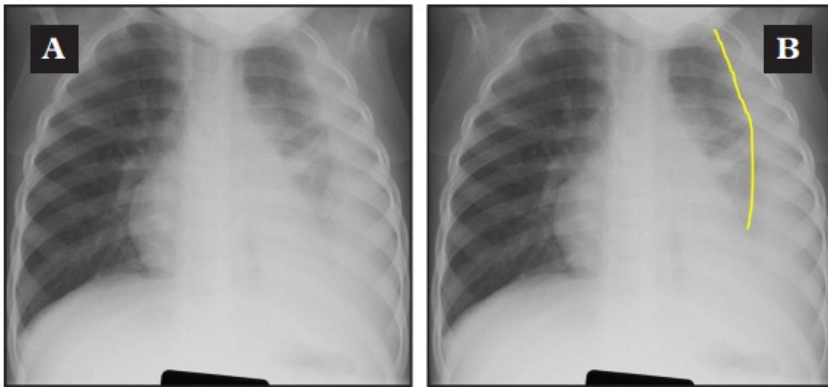
CXRs (A) and (B) are a set of anterior to posterior (AP) and lateral CXRs taken from a 4-year old child. CXRs (C) and (D) are annotated versions of the same set of CXRs. There is segmental opacification of the right lower lobe, with right-sided paratracheal lymph nodes. This indicates radiologically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



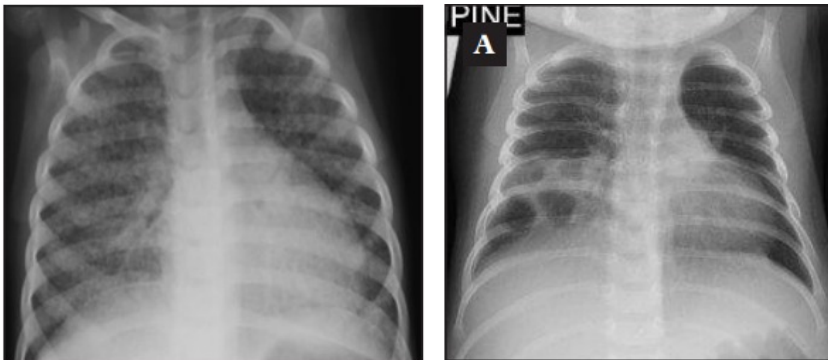
CXR (B) is an annotated version of CXR (A), taken from a 3-year-old child. Note that the right hilum appears full, with an outwardly bulging opacity that is suggestive of an enlarged right hilar lymph node. Note also the bilateral narrowing of the airways due to pressure exerted by the enlarged perihilar 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 of 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 this AP film but may be clear on a lateral film. This indicates radiologically **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 a 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.

Notes: CXR abnormalities of PTB in children living with HIV are similar to those in HIV-negative children. See Appendix 3 for a summary of CXR findings indicative of severe and non-severe disease¹.

¹Source: Diagnostic CXR Atlas for Tuberculosis in Children: A Guide to Chest X-Ray Interpretation, The Union, 2022

Testing for TB infection

A positive test that indicates infection with *M. tuberculosis* (TB bacilli) can be useful to support a diagnosis of TB in children with clinical features suggestive of TB who are bacteriologically negative or those who cannot provide a sample for laboratory testing.

Infection tests reveal the presence of an immune response and include WHO-approved skin testing and interferon-gamma release assays (IGRAs); these require a blood sample to be sent to a laboratory that is equipped to perform the test.

A positive result on an infection test is particularly useful when there is no positive contact history to indicate exposure.

A tuberculin skin test (TST) is positive:

- If ≥ 10 mm regardless of BCG immunisation
- If ≥ 5 mm in HIV-infected or severely malnourished children.

All tests for TB infection have accuracy and feasibility limitations; it should be noted that:

- A positive result does not distinguish between TB infection (“latent”) and active TB (disease)
- A negative test for infection does not exclude TB disease
- Tests can be costly and difficult to access.

HIV testing

Routine HIV testing should be offered to all children and adolescents being screened for presumptive TB or diagnosed with TB

A negative HIV test raises the likelihood that persistent symptoms are attributable TB.

Early and accurate detection of HIV infection is important for the integrated management of TB-HIV infection.

All children and adolescents with HIV infection should receive antiretroviral therapy (ART) and cotrimoxazole preventive therapy (CPT).

All children and adolescents living with HIV should be provided with comprehensive care, including family-based care.

Limitations of TB diagnostics in children

All of the above diagnostic investigations for TB in children have recognised limitations.

Tests for infection (TST or IGRAs) are often unavailable in primary or secondary healthcare settings, do not distinguish between TB infection and disease and negative results do not rule out TB as a possible diagnosis.

CXR is commonly used to support a clinical diagnosis of pulmonary TB in children. However, abnormalities in children with PTB are often non-specific, meaning that children with other common forms of lower respiratory tract infections (or pneumonia) can have similar abnormalities.

Xpert or other molecular WHO-approved diagnostic tests (of which Xpert Ultra is the most sensitive) is the recommended first-line diagnostic test for all persons with presumptive TB. However, as Xpert is likely to be positive in only one-third of children with TB, **a negative rapid diagnostic test result does not rule out TB.**

An advantage of the WHO-approved diagnostic tests is that these provide additional and rapid information about drug (rifampicin [RIF]) resistance and should be used when DR-TB is suspected in a child or adolescent.

Xpert® MTB/XDR has recently been introduced to expand testing for resistance for mutations that confer resistance to isoniazid, fluoroquinolones, ethionamide and aminoglycosides.

For children with EPTB, rapid molecular diagnostic testing provides a high positive yield from lymph node aspiration and cerebrospinal fluid (CSF), but not from pleural, pericardial or peritoneal fluid. Again, a negative rapid diagnostic test result does not rule out the diagnosis of TB.

The diagnostic yield of **AFB sputum smear microscopy** obtained by any method in young children with TB is lower than for molecular rapid diagnostic tests or culture. *However, smears may still be used in remote primary care settings where there is no alternative diagnostic available.*

As molecular rapid diagnostic tests can **detect dead** bacilli, these should **not be used** to determine **treatment response**. Smear microscopy should be used instead to follow-up response in children and adolescents with bacteriologically confirmed TB.

Extra-pulmonary tuberculosis (EPTB)

Extra-pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs and intrathoracic lymph nodes, which are commonly enlarged in children with PTB.

EPTB is common in children, in whom presentation varies with age. Table 1 lists typical clinical features of different forms of EPTB and suggested investigations for each site of disease. Symptoms vary depending on the site of disease and are characteristically persistent, progressive and may be associated with weight loss, poor weight gain and fever.

The following factors should be taken into account in the clinical assessment of children with presumed EPTB:

- **History of contact** (see above): Time lapse from exposure to disease presentation can be quite variable: it is shorter for young children with disseminated disease, longer for other forms that present in school-aged children.
- **Sputum testing and CXR:** As children with EPTB can also have PTB, sputum collection (expectorated or induced sputum, nasopharyngeal or swallowed aspirate, such as gastric aspirate, or stool) and CXR should be considered.
- **TB meningitis** 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. Important treatment decisions include choice of regimen and drug dosages. Management of complications, such as seizures, is also important.
- **HIV status:** testing is recommended if status is unknown; HIV-related care should be ensured.
- EPTB may be due to DR-TB. Contact history and history of previous TB treatment are important in determining if this is the case.
- Patients who may need further investigations/imaging (e.g., pleural or pericardial tap) that may not be possible at primary care should be referred.
- Non-severe forms of lymph node TB and pleural TB can be managed at the primary care level; however, other forms of EPTB will usually require referral, with initial hospitalisation for further investigations and specific management, including specialist involvement.

Table 1 Typical clinical features of EPTB and suggested investigations

Site of EPTB	Typical clinical presentation	Investigation	Comment
TB adenitis	<ul style="list-style-type: none"> Asymmetrical, painless, non-tender lymph node enlargement for >1 month ± discharging sinus Most commonly in the neck 	<ul style="list-style-type: none"> Fine-needle aspiration when possible for rapid molecular testing (if available) and histology TST usually positive - not necessary for diagnosis CXR Ultrasound if available 	<ul style="list-style-type: none"> Treat If axillary node enlargement on same side as BCG vaccine, consider BCG disease and refer
Pleural TB	<ul style="list-style-type: none"> Dullness on percussion and reduced breath sounds ± chest pain No acute illness 	<ul style="list-style-type: none"> CXR Ultrasound if available TST Pleural tap* 	<ul style="list-style-type: none"> Treat If pus in pleural tap, consider empyema and refer
Usually young (<5 years) with disseminated disease and severely ill			
TB meningitis	Headache, irritability/abnormal behaviour, vomiting (without diarrhoea), lethargic/reduced level of consciousness, convulsions, neck stiffness, bulging fontanelle, cranial nerve palsies	<ul style="list-style-type: none"> Lumbar puncture obtain CSF* CXR 	Hospitalise for TB treatment†
Miliary TB	Non-specific, lethargic, persistent fever, wasted	<ul style="list-style-type: none"> CXR 	Treat and refer†
Usually ≥5 years			
Abdominal TB	Abdominal swelling with ascites or abdominal masses	<ul style="list-style-type: none"> Ascitic tap CXR 	Refer†
Spinal TB	<ul style="list-style-type: none"> Deformity of spine May have lower limb weakness/paralysis/unable to walk 	<ul style="list-style-type: none"> X-ray spine 	Refer†
Pericardial TB	<ul style="list-style-type: none"> Cardiac failure Distant heart sounds Apex beat difficult to palpate 	<ul style="list-style-type: none"> CXR Cardiac ultrasound Pericardial tap* 	Refer†
TB bone and joint	<ul style="list-style-type: none"> Swelling end of long bones with limitation of movement Unilateral effusion of usually knee or hip 	<ul style="list-style-type: none"> X-ray bone/joint Joint tap* 	

EPTB = extra-pulmonary TB; TST = tuberculin skin test; CXR = chest X-ray; BCG = bacille Calmette-Guérin; CSF = cerebrospinal fluid.

*Typical findings: straw coloured fluid, exudate with lymphocytic predominance and high protein; sample could be sent for rapid molecular diagnostic testing and culture.

†Referral may be necessary for investigation and laboratory support, as well as clinical care. If all options for referral have been explored and referral is not possible, start TB treatment. **If TB meningitis is suspected, start TB treatment immediately with recommended regimen for TB meningitis.**

TB adenitis

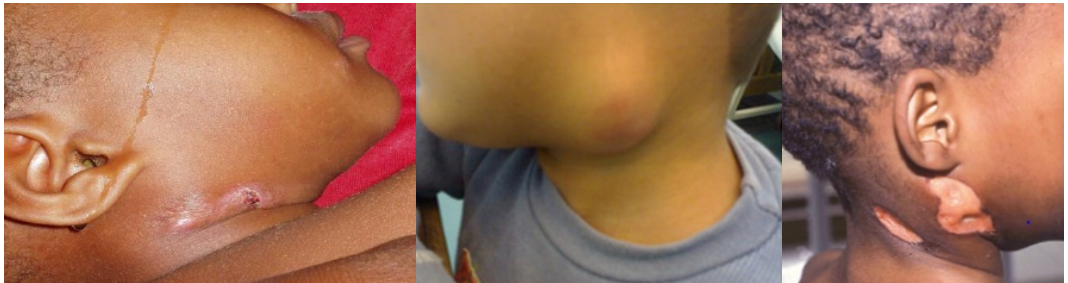
Tuberculous lymphadenitis is the most common form of EPTB in children. Lymphatic drainage from the site of infection causes enlargement of regional lymph nodes following infection. TB adenitis may or may not be associated with other symptoms of TB. Sinus and discharge may develop.

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 and not just palpable
- Painless, firm and asymmetrical - often multiple, discrete or matted
- Persistent (>1 month) and not responsive to other treatments such as antibiotics.

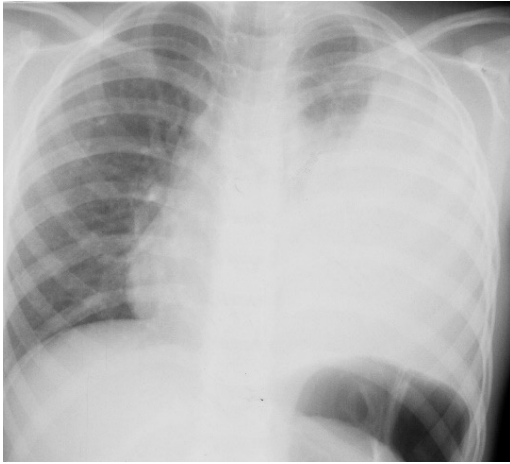
TST (if available) is usually strongly reactive but not necessary for diagnosis. Fine-needle aspiration for rapid molecular assays and histology or culture should be performed whenever possible.



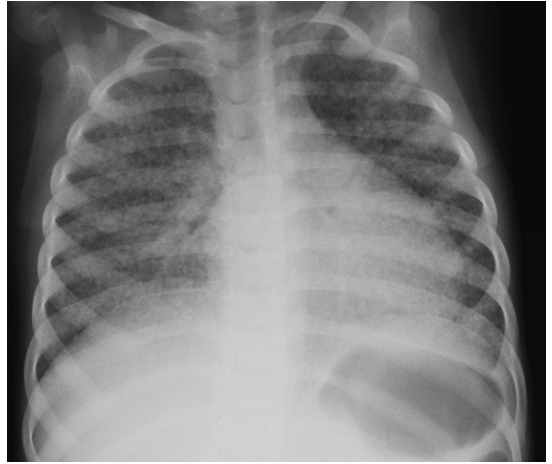
Images of TB adenitis: TB adenitis may require differentiation from bacterial or suppurative lymphadenitis, which is also usually asymmetrical but typically:

- Warm and tender
- Soft and fluctuant
- Releasing purulent fluid on lymph node aspiration
- Responsive to antibiotics ± drainage.

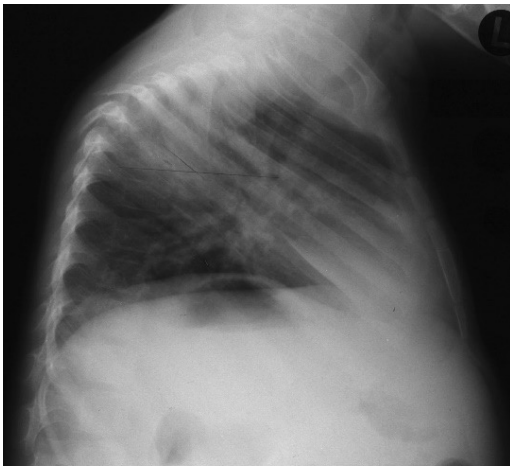
CXR abnormalities seen in children with EPTB



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



Miliary 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

Management of tuberculosis: assessing disease severity

The severity of disease at the time of diagnosis and treatment initiation affects choice of treatment regimen, treatment response and final treatment outcome. All children with TB should be assessed for disease severity in order to determine:

1. **Need for hospitalisation/referral** (see page 35) for care and/or further investigation;
2. **Treatment duration and dosage.**

Table 2 (page 32) gives the current WHO-recommended treatment options for clinically diagnosed and confirmed drug-susceptible TB. Tables 3 and 4 (page 33) show the recommended doses by weight.

For children of ≥ 3 months, the 4-month **2HRZ(E)/2HR*** treatment regimen may now be recommended by the NTP for non-severe forms of drug-susceptible TB, which is defined as:

- Lymph node TB that is peripheral (e.g., neck swelling) and isolated (no evidence of TB elsewhere);
- Uncomplicated PTB on CXR (see Appendix 3), i.e., lymph node enlargement without airway obstruction or non-cavitary disease confined to less than one full lobe of the lungs and without miliary pattern; and
- Uncomplicated TB pleural effusion.

The standard **6-month treatment regimen** should be used for:

- Children of all ages with severe PTB disease presumed or proven to be drug-susceptible. This includes intrathoracic lymph node enlargement with airway compression, cavitations or extensive lung disease with more than one lobe involved on CXR (see Appendix 3);
- Infants aged 0–2 months with PTB or lymph node TB, irrespective of severity; and
- Smear-positive TB with four drugs in the intensive phase (2HRZE/4HR).

Note that ethambutol (EMB, E) is not always required, especially in young children. EMB is recommended for the intensive phase of treatment in settings with a high prevalence of HIV or of INH resistance. EMB is also indicated to treat PTB with a high bacillary load (bacteriologically confirmed or with cavities), usually in adolescents and adults, or in those with severe forms of EPTB.

*H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment.

TB meningitis presumed to be drug-susceptible can be treated with:

- Standard 12 months' regimen (2HRZE/10HR); or
- Intensive regimen of four drugs for 6 months (6HRZETH), with higher dosages of INH and RIF and ETH replacing EMB.

The 12-month regimen comprising 2HRZE/10HR is recommended for osteo-articular TB, which includes spinal TB. Except for non-severe peripheral lymph node TB, all other forms of EPTB can be treated for 6 months with 2HRZ(E)/4HR.

Table 2 WHO-recommended treatment regimen options for new patients with drug-susceptible TB

Age and severity of TB	Recommended regimen	
	Intensive phase	Continuation phase
Pulmonary TB		
Young infants aged <3 months		
PTB of any severity	2HRZ(E)	4HR
Children and young adolescents aged 3 months - 15 years		
Non-severe PTB	2HRZ(E)	2HR
Severe PTB	2HRZ(E)	4HR
Older adolescents aged 16 - 19 years		
PTB of any severity	2HRZE	4HR
Alternative for PTB	2HPZM	2HPM
Extra-pulmonary TB		
Young infants aged <3 months		
Isolated peripheral LN disease	2HRZ(E)	2HR
Children and adolescents aged 3 months - 19 years		
Isolated peripheral LN disease	2HRZ(E)	2HR
Osteo-articular TB	2HRZE	10HR
TB meningitis standard	2HRZE	10HR
TB meningitis intensive	6HRZETH	
All other forms of EPTB	2HRZ(E)	4 HR

Continuation phase

INH, H=isoniazid; RIF, R=rifampicin; PZA, Z=pyrazinamide; EMB, E=ethambutol; P=rifapentine; M=moxifloxacin; ETH= ethionamide. Numeral refers to number of months of the regimen. For example, 2HRZE refers to 2 months of daily INH, RIF, PZA and EMB.

PTB = pulmonary TB; LN = lymph node; EPTB = extra-pulmonary TB.

Table 3 Recommended dosages for children by weight

Drug	Daily dosage in mg/kg	Range in mg/kg (maximum dosage)	Dose range for TBM short intensive course in mg/kg (6HRZETH)
Isoniazid (H, INH)	10*	7–15 (300 mg)	15–20
Rifampicin (R, RIF)	15*	10–20 (600 mg)	22.5–30
Pyrazinamide (Z, PZA)	35	30–40 (2,000 mg)	35–45
Ethambutol (E, EMB)	20	15–25 (1,200 mg)	Not recommended
Ethionamide (ETH)	17.5†		17.5–22.5 (1,000 mg)

TBM = tuberculous meningitis.

*Recommended dosages for children are higher (as shown above) than for adolescents and adults for INH: 5 mg/kg for ≥10 years; and RIF: 10 mg/kg for ≥10 years.

† Ethionamide to be used in TBM (and in patients who are ≥6 years and treated with shorter all-oral bedaquiline-containing regimens for multidrug-resistant TB).

Table 4 Numbers of tablets by weight band for fixed-dose combinations

Weight bands kg	Number of tablets		Continuation phase
	Intensive phase		
	HRZ	E*	HR
	50/75/150	100	50/75
4–7	1	1	1
8–11	2	2	2
12–15	3	3	3
16–24	4	4	4
	HRZE 75/150/400/275		HR 75/150
25–29	2		2
30–34	3		3
35–64	4		4
>65	5		5

* E should be added in the intensive phase for children or adolescents with extensive or multi-bacillary (such as smear-positive) disease.

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol.

Tuberculosis treatment: some general rules

- Treatment regimens by disease category are listed in Table 2 on page 32;
- Dosages are determined by weight (mg/kg). Higher doses are recommended for children (usually <25 kg) than adolescents and adults in mg/kg for some drugs;
- Drug dosages by weight are presented in Table 3 on page 33;
- Number of tablets by weight bands are presented in Table 4 on page 33;
- Dispersible fixed-dose combination formulations are available for young children;
- Four drugs are required in the intensive phase for children and adolescents living with HIV with sputum smear-positive PTB or with severe disease;
- All children receiving TB treatment should be registered in the health unit TB register;
- Diagnostic category, treatment regimen and date of commencement should be recorded in road-to-health/child health card or booklet, TB treatment card and health unit TB register;
- Weight is important for monitoring treatment response. Weight should be recorded at each visit in road-to-health/child health card or booklet and TB treatment card;
- Children gain weight while receiving TB treatment and drug dosages should be adjusted accordingly;
- Once treatment is started, it must be completed; “trial TB treatment” should NOT be used as a diagnostic tool;
- A caregiver should be identified as the treatment supporter for children of all ages, including older children and adolescents;
- Adherence to the full course of treatment should be emphasised and reinforced;
- Treatment outcomes for children completing treatment are generally excellent. Most deaths occur in those who do not receive treatment;
- TB drugs are usually very well tolerated in children, but accurate dosages as recommended by weight are critical for safety;
- Adverse events (side-effects) are unusual and the most important is hepatotoxicity;
- **Follow the national TB treatment guidelines at all times.**

DO NOT USE CXR TO MONITOR TREATMENT RESPONSE

Additional management decisions

- Hospital admission for inpatient care and investigations (see also Appendix 1) are advised in case of:
 - Severe forms of PTB and EPTB for further investigation and initial management
 - Presence of danger signs (for e.g., reduced level of consciousness or recurrent/prolonged seizures)
 - Severe pneumonia (for e.g., fast breathing and chest indrawing)
 - Asymmetrical/persistent wheezing
 - Severe malnutrition for nutritional rehabilitation
 - Other comorbidities (for e.g., severe anaemia)
 - Restlessness, irritability or lethargy
 - Newborns
 - Severe adverse reactions, such as hepatotoxicity
- For all HIV-infected children, ensure that the following are provided:
 - CPT
 - ART
 - Family-based care/screening
- Referral should be considered in case of:
 - Diagnostic uncertainty
 - Need for HIV-related care, such as commencement of ART
 - MDR-TB contact
 - Presumptive DR-TB due to unsatisfactory treatment response despite good adherence to TB treatment.
- Nutritional support should be provided for malnourished children if available.
- Breastfeeding infants and children should continue to be breastfed while receiving TB treatment.
- Pyridoxine is not routinely given but is recommended for severely malnourished and HIV-infected children.
- In patients with TB meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.

Follow-up and monitoring of tuberculosis treatment in children and adolescents

This is a critical part of effective TB treatment and requires a clear management plan and TB treatment card. Follow-up and monitoring should be as follows:

Non-HIV-infected: to be reviewed monthly during the intensive phase and bi-monthly during the continuation phase

HIV-infected: to be reviewed at 2 weeks and 4 weeks following commencement of TB treatment and then monthly until treatment is completed. Follow-up to be aligned with HIV treatment and care.

Treatment outcomes are determined at the end of treatment, at 4 months for the short regimen, at 6 months for the standard regimen and 12 months for the longer regimen.

Health education

It is important to explain and emphasise to both the caregiver and the child why they must take the full course of treatment even if they are feeling better.

Caregivers and children should be reassured that TB drugs in children are well tolerated and safe.

THE MOST IMPORTANT ADVERSE EFFECT IS HEPATITIS, WHICH USUALLY PRESENTS WITH JAUNDICE, NAUSEA AND VOMITING. THERE MAY BE ABDOMINAL PAIN, JAUNDICE; THE LIVER MAY BE TENDER AND ENLARGED

IF ADVERSE EFFECTS ARE SUSPECTED, STOP THE TB DRUGS IMMEDIATELY AND REFER TO HOSPITAL

Evaluating treatment response

Symptomatic improvement and weight gain are markers of treatment response.

Measuring and recording weight: dosages should be adjusted depending on weight gain.

Adherence assessment and support: treatment card should be reviewed and discussed with the patient, caregivers and other treatment supporters. Risk factors for poor adherence, such as distance from clinic/hospital to residence, poor transport facilities, being an orphan, ill health of primary caregiver, being an adolescent, or having comorbidities, such as living with HIV requiring additional medication should be noted.

Follow-up sputum samples should be collected for smear microscopy 2 and 5 months after the start of treatment and at treatment completion from adolescents who were bacteriologically confirmed at diagnosis.

Repeat sample collection at 2 months in children without bacteriologically confirmed TB is not indicated unless there is an inadequate clinical response.

If there is unsatisfactory response to treatment, such as persistent symptoms, lack of weight gain or a positive follow-up smear, adherence should be assessed and the patient referred in order to evaluate for drug resistance and other causes of poor treatment response.

Follow-up CXR is not needed if the child is responding well to TB treatment. Children commonly have slow radiographic response to treatment and may have persistent radiographic abnormalities at treatment completion, but this does not indicate lack of response to treatment.

Treatment interruption

It is very important to emphasise to the caregiver(s) that it is necessary to complete all TB treatment even after the child starts feeling well in order to avoid relapse and/or development of drug resistance. Should treatment interruption occur, these recommendations should be followed:

- i) Interruption during the intensive phase of the 4–6-month regimens
 - If interruption <14 days, treatment is continued and remaining doses completed
 - If ≥14 days, intensive phase should be restarted.
- ii) Interruption during continuation phase of the 4-month 2HRZ(E)/2HR regimen
 - If ≥80% of doses have been completed within 2 months, further treatment is not necessary
 - If <80% doses have been completed and the total number of interrupted days is <1 month, the remaining doses are to be completed
 - If <80% of doses have been completed and total number of interrupted days is ≥1month, treatment to be restarted from beginning of intensive phase.

iii) Interruption during continuation phase of the 6-month 2HRZ(E)/4HR regimen

- If $\geq 80\%$ of doses have been completed within 4 months, further treatment is not necessary
- If $< 80\%$ doses have been completed and total number of interrupted days is < 2 months, the remaining doses are to be completed
- If $< 80\%$ of doses completed and total number of interrupted days is ≥ 2 months, treatment are to be restarted from beginning of intensive phase.

Poor treatment response

Most children with TB will start to show signs of improvement after 2–4 weeks of TB treatment.

Poor adherence is a frequent cause of poor treatment response.

Based on assessment at 1–2 months after treatment initiation, unsatisfactory treatment response should be considered if there is:

- No resolution of symptoms or symptoms are getting worse;
- Continued weight loss;
- Sputum smear positivity at 2-month follow-up.

If treatment adherence is satisfactory, poor treatment response suggests the possibility of DR-TB; this will require careful assessment.

IN CASE OF POOR TREATMENT RESPONSE, REFER FOR FURTHER ASSESSMENT

Contact screening and management

Contact screening should be routinely conducted and has two purposes:

- Detection and treatment of a contact of any age with active TB
- Provision of TB preventive treatment (TPT) for all eligible contacts.

All contacts with symptoms should be carefully assessed for TB.

In contact screening, household and other close contacts of a person (usually an adolescent or adult) with bacteriologically confirmed PTB are prioritised.

Contact management consists of identification and line listing of close contacts, their clinical evaluation, testing and provision of appropriate TB treatment for people with TB or TPT for people without TB. Reverse contact tracing refers to identifying the source case for children diagnosed with TB.

Important questions for any person commenced on TB treatment

- i. Does the index patient have bacteriologically confirmed TB?**
- ii. What treatment regimen is the index patient receiving and what is the treatment response?**
- iii. Who lives in the household?**
- iv. What are the ages of the household contacts?**
- v. Are the contacts sick or well?**

List specific details of all contacts and their management in the contact register

- All close contacts of bacteriologically confirmed PTB patients should be screened for TB.
- If the TB source case is the child's parent and is HIV-infected, it is important to ensure that HIV status of other children is known and if this is not the case, offer HIV testing and counselling.
- Symptom screening can be initiated at the primary or community care level.
- Symptoms alone are used to screen child (<10 years) contacts for TB.
- Screening of symptomatic adolescent contacts should include sputum investigations and CXR (if available) to rule out active TB before initiating TPT.
- Symptom screen involves assessment for presence of any cough, fever, poor weight gain/weight loss or night sweats in the past 3 months.

Refer to Appendix 4 for the approach recommended for the assessment of child and adolescent contacts.

Tuberculosis preventive treatment

TPT is recommended for children and adolescents who are household or close contacts of a case with bacteriologically confirmed TB AND who do not have evidence of TB disease:

- Children (<10 years) who are well with a negative symptom screen
- Non-HIV-infected adolescents (10–19 years) with a negative symptom screen and normal CXR (if available)
- HIV-infected children or adolescents with a negative symptom screen.

Note that evidence of infection (positive TST or IGRA) is desirable when offering TPT to older contacts aged ≥ 5 years. If TB infection test is unavailable, TPT can still be given.

The choice of TPT regimen depends on the age of the child/adolescent, the HIV status and ART regimen administered and the availability of suitable child-friendly formulations. The effectiveness of shorter regimens are similar to that of six months of isoniazid (6H), with better adherence and fewer side effects. Current WHO-recommended TPT regimen options and dosages for contacts are listed in Tables 5 and 6.

Table 5 TPT regimen options for contacts of persons with drug-susceptible TB

TPT regimen		Comment
6H	Six months of daily INH	Especially suitable for children and adolescents living with HIV* and receiving ART
3HR	Three months of daily INH and RIF	Suitable for non-HIV-infected children <25 kg if dispersible FDCs available
4R	Four months of daily RIF	Suitable for non-HIV-infected children and adolescents 5-19 years
3HP	Three months of weekly INH and RPT	Not yet recommended for child <2 years, as the use of currently available preparations may be challenging for young children. However, this may change as recommended dosage data and child-friendly preparations of RPT become available
1HP	One month of daily RPT and INH	Not currently recommended for children <13 years

TPT = tuberculosis preventive treatment; INH, H = isoniazid; ART = antiretroviral therapy; RIF, R = rifampicin; FDC = fixed-dose combination; RPT, P = rifapentine.

*Rifampicin- and rifapentine-containing regimens should be prescribed with caution in children and adolescents living with HIV and on ART because of potential drug–drug interactions. They can be used with efavirenz-based ART regimens.

Table 6 Recommended dosages for TPT regimens by weight band and available formulations

Weight bands kg	3HR 50/75 mg dispersible FDC	6H 100 mg tablet	4R 300 mg tablet	3HP H 100 mg, P 150 mg tablets	
4–7.9	1	0.5	–	–	–
8–11.9	2	1	–	–	–
12–15.9	3	1.5	–	3	2
16–24.9	4	2	1	5	3
	75/150 mg dispersible FDC	300 mg tablet	300 mg tablet	H 300 mg, P 300 mg tablets	
25–29.9	2	1	1	2	2
≥30	3	1	2	3	3

TPT = tuberculosis preventive treatment; H, INH = isoniazid; R, RIF = rifampicin;

FDC = fixed-dose combination, P, RPT = rifapentine.

Notes: For children <4 kg, refer to a specialist.

3HP is currently not recommended for children <2 years and results in a high pill burden.

1HP use is currently limited to older adolescents and adults ≥13 years and the recommended dosage regardless of weight band is INH 300 mg and RPT 600 mg daily.

Challenges for preventive therapy

It is necessary to create greater awareness about the rationale, safety and need for TPT completion. It takes time and understanding to explain to caregivers and families why children should take up TPT to protect them from developing TB. It is challenging for parents (and many health workers) to understand that a child who is well needs to take medicine every day for up to 6 months. It is challenging to ensure that the child completes the full course for the same reasons. A higher rate of treatment completion is an advantage of the shorter TPT regimens. There are also often concerns about the potential toxicity of TPT regimens; however, the risk of serious toxicity due to TPT is extremely low and much lower than the risk of the child developing TB.

Specific TPT recommendations for contacts of people with MDR-TB require further evidence. The risk of infection and disease is likely to be similar as for other TB contacts. Therefore, TPT regimens that include a drug to which the source case with MDR-TB is susceptible, such as daily levofloxacin for 6 months, is increasingly used for high-risk contacts without disease.

Follow-up is critical

Those on a 3-month TPT regimen and those receiving a 6-month regimen should be reviewed every month and every 2 months, respectively. The need to complete the treatment should be reinforced each time.

If TB symptoms develop, the patient should be investigated for TB, TPT stopped and appropriate TB treatment initiated, if necessary.

Drug-resistant tuberculosis in children

MDR/RR-TB is defined as TB that is resistant to at least RIF and usually to both RIF and INH. With increasing numbers of people with MDR/RR-TB worldwide, there is also an increasing number of children with MDR/RR-TB. The prevalence of MDR/RR-TB in a community determines how common it is in children in the same community.

The clinical presentation of DR-TB in a child or adolescent is similar to the clinical presentation of other forms of TB (as above). The diagnosis is therefore often made on clinical and radiological grounds as bacteriological confirmation is not always possible. A high index of clinical suspicion is required in children who fit the criteria listed below.

Important criteria for suspected DR-TB in children:

- Close contact with a person with known/confirmed DR-TB
- Contact with a person with presumed DR-TB (source case did not respond to treatment or is currently being retreated for TB or recently died from TB)
- Child has been on first-line treatment but has failed to improve clinically following 2 months of treatment despite good adherence, with persistence of symptoms failure to gain weight or persistence of sputum smear positivity
- Child previously treated for TB (especially within the past 12 months) presents with recurrence of disease (either a true relapse or reinfection).

Samples for bacteriological confirmation should be collected whenever possible. Molecular rapid diagnostic tests such as **Xpert MTB/RIF** or **Truenat** provide rapid information about RIF resistance. Samples with RIF resistance should be sent for **culture and drug susceptibility testing** or tested using **Xpert MTB/XDR**, which tests for resistance to INH and some second-line drugs such as fluoroquinolones and ethionamide.

If the child is in close contact with a person who has failed TB treatment or is non-adherent to TB treatment, it is important to obtain information on whether this person has been confirmed as having DR-TB and the drug resistance profile.

When treated appropriately, outcomes in children with MDR/RR-TB are generally good, with high cure rates. However, treatment for DR-TB is more complicated than treatment for drug-sensitive TB, as more drugs are required and there is a greater risk of serious adverse drug reactions. Treatment regimens are becoming shorter, safer, more acceptable (all-oral) and less costly with novel drugs such as bedaquiline and delamanid now being recommended for use in children of all ages. However, a child with suspected DR-TB requires referral to a centre with available diagnostics and management experience and expertise.

Screening of household contacts of a person with DR-TB is strongly recommended. All contacts should be carefully evaluated for TB disease. High-risk contacts without active TB should be considered for TPT that includes a drug to which the source case with MDR-TB is susceptible after consultation with specialist services.

Children and adolescents living with HIV

Children and adolescents living with HIV have an increased risk of TB exposure and infection, and greater likelihood of progression to disease and TB-related morbidity and mortality. This risk depends on the degree of immune suppression.

Diagnosis of tuberculosis in children and adolescents living with HIV

Diagnosis of TB in children and adolescents living with HIV can be more challenging than in HIV-negative individuals because:

- Clinical features consistent with PTB are common in children living with HIV but may be caused by other diseases and are not specific to TB; therefore diagnosis can be a challenge.
- Children and adolescents living with HIV have a very high incidence of acute and chronic lung diseases other than TB.
- Children and adolescents living with HIV may have lung disease due to more than a single cause (coinfection), which can mask response to treatment.
- There is an overlap of radiographic findings in TB and other HIV-related lung diseases.
- Most children living with HIV have been infected via mother-to-child transmission. HIV prevalence is highest among children <5 years. This is also the age group for which it is most difficult to confirm the cause of acute or chronic lung disease, including TB.
- As for all children with presumptive TB, bacteriological confirmation should be sought whenever possible although yield is low in HIV-infected children.
- TST is less sensitive in children and adolescents living with HIV than in HIV-negative children and adolescents. Induration of ≥ 5 mm is considered positive if the child is living with HIV.

Management of tuberculosis in children and adolescents living with HIV

A comprehensive approach to management of both TB and HIV is critical.

- HIV testing is indicated in all children with presumed and confirmed TB unless their HIV status is already known.
- Approach to TB diagnosis is similar to that for non-HIV-infected children.
- Treatment for TB in children or adolescents living with HIV is also based on site of TB, weight and severity of TB disease (pages 32 and 34).
- All children living with HIV and TB should receive CPT and ART.
- ART should be started within 2 weeks of initiating TB treatment.
- Nutritional support is often needed for children with both HIV and TB.
- All children and adolescents living with HIV should be screened for TB at every attendance using the following symptom screen: (any) cough, fever, poor weight gain or close contact with a person with TB. If they gave any one of these symptoms, they should be investigated for TB.
- All children and adolescents living with HIV who are household contacts of people with bacteriologically confirmed TB should be evaluated for TB and either treated for TB or given TPT if they are found not have TB.
- All children aged ≥ 12 months living with HIV who are unlikely to have TB should receive TPT as part of comprehensive HIV care, regardless of history of TB contact.
- Co-located services for children with HIV and TB should be available and follow-up care should be aligned to reduce the number of visits to health facilities.
- Family members should be counselled and tested for HIV and screened for TB. The specific needs of each family should be determined and a plan of action developed to ensure that the family receives comprehensive care.

Management of babies born to women with tuberculosis

- If the newborn of a mother with TB is unwell, the child should be referred to a specialist for further evaluation and prompt treatment initiated if TB is confirmed or likely.
- The mother should receive effective TB treatment so that she is no longer infectious.
- Infection prevention and control measures should be in place in the hospital nursery and at home.
- If the newborn is well and has no symptoms or signs of TB, TPT (preferably 3HR) should be provided and BCG vaccination delayed until TPT is completed.
- If the infant is exposed to HIV and is on nevirapine, 6H is the preferred TPT regimen.
- At completion of TPT, TST should be performed. If the TST result for TB infection is negative or unavailable, BCG should be provided. If the test is positive, BCG is not required.
- If the mother is taking TB medicines, she can safely breastfeed the baby who is receiving TPT. All mothers living with HIV should be offered ART to reduce risk of vertical transmission.
- Neonates born to women of negative or unknown HIV status should receive BCG.
- Neonates born to HIV-infected mothers should not receive BCG until the infant is clinically and immunologically stable on ART.
- Neonates born to women of negative or unknown HIV status should receive BCG.
- Neonates born to HIV-infected mothers should not receive BCG until the infant is clinically and immunologically stable on ART.

BCG vaccination

BCG vaccination is provided to newborns as part of the national immunisation programme. It provides strong protection against the development of severe forms of TB in early childhood, including TBM and miliary TB. Neonates born to women of negative or unknown HIV status should receive BCG. Newborns or infants with HIV infection should not receive BCG vaccination until clinically and immunologically stable on ART.

Severe reactions to BCG include BCG lymphadenitis and disseminated BCG disease; these children should be referred for specialised care.

National tuberculosis programme management issues

Most of the issues that relate to an effective NTP providing high-quality TB care and prevention relate to children and adolescents, as well as adults. Early case detection and effective management of people with TB in the community will reduce the burden of TB in children.

It is important for NTPs to cover child and adolescent TB during funding and resource allocation, in strategic and action plans, policies and Guidelines, and integrate child and adolescent TB into training, capacity building, mentorship and supervision activities. NTPs should have a focal person for child and adolescent TB and a technical working group for child and adolescent TB to support implementation of services, recording and reporting, and monitoring and evaluation.

Registration, recording and reporting

All children and adolescents investigated for TB need to be recorded in the presumptive TB register.

All children and adolescents found to have TB should be initiated on appropriate treatment and be registered in the TB register. They should be part of the quarterly and yearly cohort analysis and reporting; bacteriological tests that are negative or not obtained should also be recorded.

Children and adolescents are reported in the same way as adults; records should include the following: age, sex, site of TB, disease category (e.g., bacteriologically confirmed, clinically diagnosed), HIV status, outcome.

Treatment outcome

It is very important that treatment outcomes are reported by the NTP for all children and adolescents who receive TB treatment following the standardised WHO treatment outcome definitions:

- i. Cured (for bacteriologically confirmed)
- ii. Treatment completed
- iii. Lost to follow-up
- iv. Died
- v. Failed (for bacteriologically confirmed)
- vi. Not evaluated.

Important NTP indicators for monitoring and evaluation include coverage of contact screening, TPT initiation in eligible groups, such as young child contacts, and TPT completion. Recording and registering children eligible for TPT provides important information for the NTP on drug requirements for procurement to avoid stock-outs, monitoring the coverage of contact screening as well as TPT uptake and completion.

Data on TB registrations, treatment outcomes and contact management, including data on TPT, should be tabulated, analysed and used quarterly to close possible gaps in TB case-finding, case retention and TB prevention cascades, and to strengthen quality of TB care and prevention services.

Engage all care providers

As part of the overall TB control activities, NTPs need to coordinate and engage all relevant care providers to ensure adequate service provision through dissemination and implementation of the International Standards of TB Care*. Public-private partnerships, including collaboration with community and faith-based organisations, are critical in reinforcing case-finding and supporting adherence.

TPT should be available at all levels of the health system. Current coverage is much higher in HIV services than in child and adolescent health services. A decentralised model of care providing community-based, integrated services will improve coverage.

Infection prevention and control

Prevention of transmission of the TB bacilli in the household and in health facilities is an important component of controlling and managing TB in children. The following simple procedures are effective in TB infection prevention and control at home and clinics:

- Early diagnosis and treatment of adults with TB in the household
- Prompt identification of potential and known people with infectious TB at the clinic; isolation and treatment of cases with minimal delay using triaging and screening
- Natural ventilation and sunlight should be maintained at all times:
 - Doors and windows should be kept open on opposite sides of the TB clinic and other clinics (effective ventilation with air changes)
 - Where children and adults stay together, windows should be kept open whenever possible
 - TB patients should be advised to do the same at home
- Provision of health education about TB transmission without stigmatising TB patients
- Ensuring proper cough hygiene both at home and in health facilities
- Cough hygiene strategies include:
 - Covering mouth and nose when coughing or sneezing
 - Using tissues and throwing them away after use
 - Washing hands or using a hand sanitiser every time you touch your mouth or nose
 - Using face masks in those with infectious TB.

Newborns are particularly vulnerable and outbreaks of TB among neonates occur in newborn care settings. The source is generally the mother or a staff member. If a mother has TB, she can breastfeed her newborn, provided she is receiving treatment for TB and uses a mask; the newborn should receive TPT if there is no evidence of TB in the newborn. In this case, BCG is delayed until after completion of TPT.

*<https://theunion.org/technical-publications/international-standards-for-tuberculosis-care>

Definitions and distinctions

Infection with *Mycobacterium tuberculosis* (also called TB bacilli) usually results from the inhalation of infected droplets exhaled by someone who has TB. The most infectious source cases are those with bacteriologically confirmed pulmonary TB (PTB). The closer the contact with the source case, the greater the exposure and greater the risk of getting infected with *M. tuberculosis*.

A person carrying the *M. tuberculosis* bacteria in the body is said to have **TB** or **tuberculous infection**. Many people have or have had TB infection, and most are well, remain healthy and do not develop TB disease. People with TB infection are not able to transmit *M. tuberculosis*.

When the bacteria in the body of a person with TB infection start to multiply and become numerous enough to damage one or more organs of the body, the person is said to have progressed to **TB disease**. This damage causes clinical symptoms and signs, and is referred to as “tuberculosis” or active TB disease.

A person who has been diagnosed to have TB using a positive laboratory test is said to have **bacteriologically confirmed TB**. The most frequently used TB tests include rapid molecular diagnostic assays, smear and culture.

A **rapid diagnostic test** in this guide refers to a molecular WHO-recommended rapid diagnostic test (mWRD) or smear microscopy when mWRD is unavailable. GeneXpert® assays and lateral flow- lipoarabinomannan are examples of rapid diagnostic tests in current use.

A **close contact** of a source case with TB disease is defined as a person living in the same household as, or in frequent contact (e.g., child minder, school staff) with the source case.

A **source case** is defined as a person with TB disease who is responsible for transmitting *M. tuberculosis* to another person or persons.

An **index case** is the first identified case of TB in a specific household or other comparable settings in which others may have been exposed to TB bacilli. This is the first person around whom TB contact investigation is initiated; she/he might not necessarily be the source of initial exposure, which may be difficult to establish.

Children: defined in this guide as those between 0 and 9 years (i.e., <10 years) of age.

Infants: defined as those in the age-group of 0-11 months (< 1 year).

Adolescents: defined as those in the age-group of 10-19 years.

Resource materials

**ALWAYS REFER TO THE NATIONAL GUIDELINES FOR TB
IN CHILDREN AND ADOLESCENTS OF YOUR COUNTRY**

1. World Health Organization. WHO consolidated Guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO, 2022. <https://www.who.int/publications/i/item/9789240046764>
2. World Health Organization. WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO, 2022. <https://www.who.int/publications/i/item/9789240046832>
3. International Union Against Tuberculosis and Lung Disease. Diagnostic CXR atlas for tuberculosis in children: a Guide to chest X-ray interpretation. Second Edition. Paris, France: The Union, 2022. <https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children>
With accompanying image library: <https://atlaschild.theunion.org/>
4. World Health Organization. WHO consolidated Guidelines on tuberculosis. Module 1: Prevention. Geneva, Switzerland: WHO, 2020. <https://www.who.int/publications/i/item/9789240001503>
5. World Health Organization. WHO TB knowledge sharing platform. Geneva, Switzerland: WHO, 2022. <https://tbksp.org>. Accessed on 25 November 2022.
6. World Health Organization. WHO OpenTB: the End TB course. Geneva, Switzerland: WHO, 2022. <https://openwho.org/channels/end-tb>. Accessed on 25 November 2022.
7. International Union Against Tuberculosis and Lung Disease. Management of tuberculosis: a Guide to essential practice. Seventh Edition. Paris, France: The Union, 2019. <https://theunion.org/technical-publications/management-of-tuberculosis-a-Guide-to-essential-practice>
8. Dongo JP, et al. Implementation of an effective decentralized program for detection, treatment and prevention of tuberculosis in children. *Trop Med Infect Dis* 2021; 6: 131.
9. Turkova A, et al. Shorter treatment for non-severe tuberculosis in African and Indian children. *N Engl J Med* 2022; 386: 911–922.

Appendix 1. Indications requiring hospital admission for inpatient care and/or for further investigations

Presence of danger signs requiring urgent medical care

- Signs of severe pneumonia or respiratory distress
- Signs of central nervous system disease, such as a reduced level of consciousness or recurrent/prolonged seizures
- Presumptive meningitis – treatment should be initiated without delay
- Signs of sepsis

Necessary for management of comorbidities

- Initiation of ART and comprehensive HIV care
- Nutritional rehabilitation for severe malnutrition
 - Other comorbidities, such as severe anaemia

Diagnostic uncertainty requiring further investigation at referral level

- Invasive procedures required for laboratory samples that cannot be performed in the current setting, such as pleural tap, lumbar puncture
- Imaging, such as ultrasound
- Possibility of an alternative diagnosis
- Presumptive drug-resistant TB

Appendix 2: Scores for clinical features with or without CXR findings*

A) Score for suggestive signs and symptoms when CXR is available

Clinical feature	Score	CXR abnormality	Score
Cough >2 weeks	+2	Cavity/cavities	+6
Fever >2 weeks	+5	Enlarged lymph nodes	+17
Lethargy	+3	Opacities	+5
Weight loss	+3	Miliary pattern	+15
Haemoptysis	+4	Effusion	+8
Night sweats	+2		
Enlarged typical lymph nodes	+4		
Tachycardia	+2		
Tachypnoea or fast breathing	+1		
Sum A: _____		Sum B: _____	

If Sum A + Sum B > 10, then treat for TB
















B) Score for suggestive signs and symptoms when CXR is not available

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 or fast breathing	+2
Sum A: _____	

If Sum A >10, then treat for TB

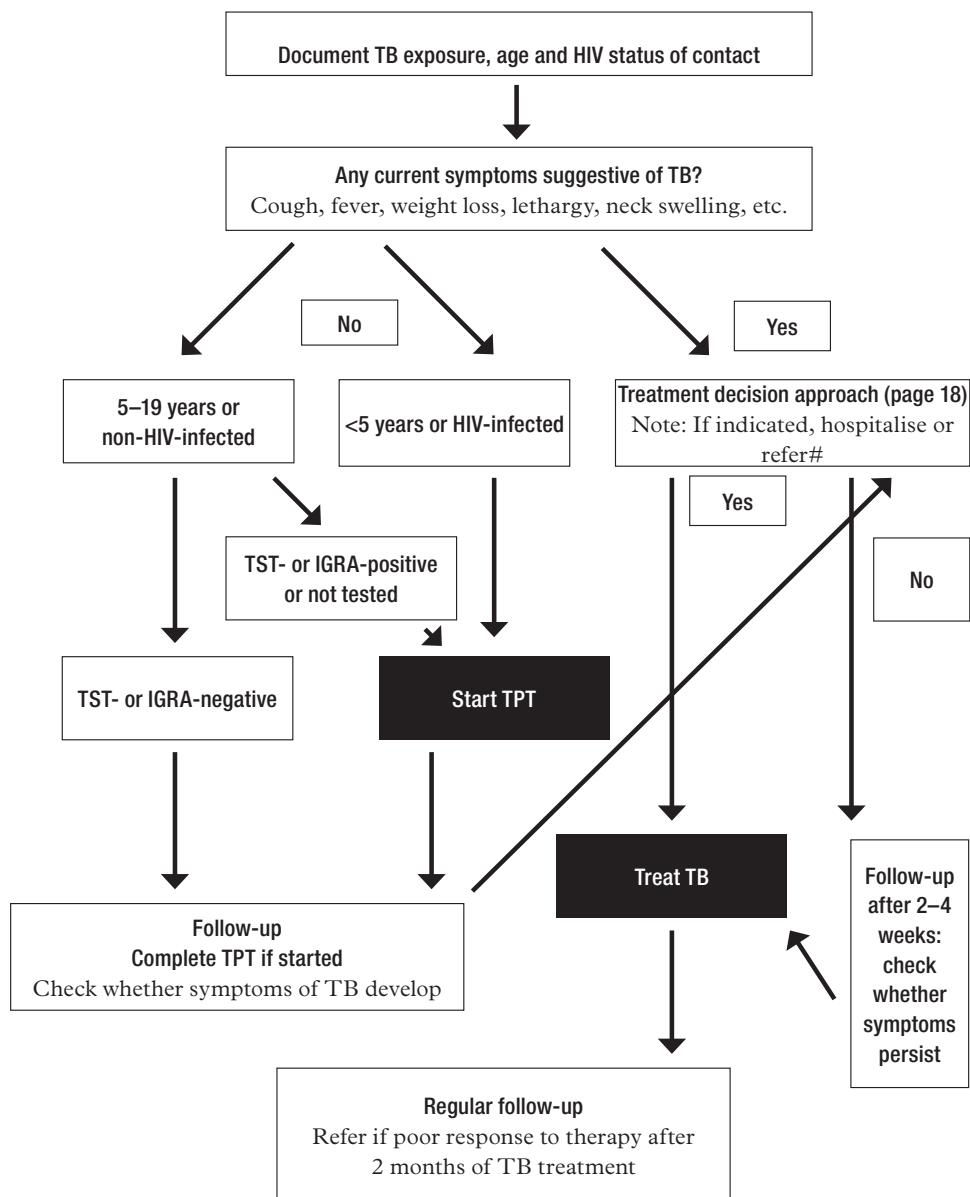
*Example from reference #2: World Health Organization. WHO operational handbook on Tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO, 2022.

Appendix 3. Classification of TB severity on CXR*

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

*From reference #3: 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.

Appendix 4. Guidance for screening and management of child and adolescent contacts*



Close contact is defined as a person living in the same household as, or in frequent contact (e.g., child minder, school staff) with a source case with PTB.

See Appendix 1.

*Adapted from reference #2: World Health Organization. WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO, 2022.

About The International Union Against Tuberculosis and Lung Disease (The Union)

The Union is a scientific, technical and membership organisation. Established in 1920, The Union strives to end suffering due to tuberculosis and lung diseases, old and new, by advancing better prevention and care. We seek to achieve this by the generation, dissemination and implementation of knowledge into policy and practice. We aim to ensure that no one is left behind, people are treated equally and we have a focus on vulnerable and marginalised populations and communities.

A health world for all, free of tuberculosis and lung disease.

ISBN: 979-10-91287-33-3