PAKISTAN CHEST SOCIETY

PAKISTAN
CHEST SOCIETY
STRIVING FOR PULMONARY CARE

Clinical Practice Guidelines

Tuberculosis

PAKISTAN CHEST SOCIETY-2026

Guidelines On

Tuberculosis

March 2026

PAKISTAN CHEST SOCIETY

PAKISTAN
CHEST SOCIETY
STRIVING FOR PULMONARY CARE

Table of Contents

Table of Contents

Preface

It gives me great pleasure to present this updated guideline on the management of tuberculosis, developed under the umbrella of the Pakistan Chest Society (PCS). This new edition builds on our earlier work and includes the latest national and international recommendations to guide healthcare professionals in the care of patients with TB.

The guidelines have been prepared through the teamwork of the PCS Tuberculosis Working Group, using the most recent evidence from the World Health Organization and the National TB Control Programme. We have tried to cover all key areas of TB care like diagnosis, treatment, follow-up, contact management, DR-TB and role of family physicians in control of TB. Our focus is on what is practical and relevant for our local healthcare system.

This guideline provides a clear and concise guide that can serve as a quick reference for pulmonologists, physicians, pediatricians, and other health professionals involved in TB management. We hope it will help standardize care and support Pakistan's national efforts to control and eventually eliminate TB.

I would like to sincerely thank all members and contributors of the Pakistan Chest Society who worked with great commitment and cooperation to prepare this document. Their efforts have made this updated guideline possible.

We hope that this resource will continue to support clinicians in providing the best possible care for patients with tuberculosis.

Message by the President
Pakistan Chest Society

Assalam-u-Alaykum,
It is a matter of great pride for the Pakistan Chest Society to present the updated PCS TB Guidelines. These guidelines reflect the hard work, dedication, and collective wisdom of our experts from across the country. TB remains a major public health challenge for Pakistan, and it is our shared responsibility to ensure early diagnosis, effective treatment, and prevention through evidence-based practice.

I am confident that these guidelines will serve as a practical resource for clinicians, helping them provide better care for our patients and improving outcomes nationwide. I am deeply grateful to all colleagues who contributed their time and expertise to this important national effort.

May Allah guide us in our mission to reduce the burden of TB in Pakistan.

Prof. Shereen Khan

President
Pakistan Chest Society

Message by the Chairman

Guideline Committee, Pakistan Chest Society

It gives me great pleasure to present the Guidelines for the Management of Tuberculosis (TB) by the Pakistan Chest Society. These guidelines aim to improve early detection, standardized treatment, and long-term control of TB—a disease that continues to affect thousands across Pakistan and remains a major public health concern.

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis, most commonly involving the lungs. Symptoms such as persistent cough, fever, night sweats, and weight loss should prompt timely evaluation. Cough for more than two weeks should raise the suspicion of TB. In Pakistan, factors like overcrowding, malnutrition, poor ventilation, smoking, and incomplete treatment courses contribute to ongoing transmission, making local awareness and vigilance essential.

The TB Working Group, led by Prof. Nisar Ahmed Rao, has adopted international recommendations to our healthcare system. These guidelines outline the importance of sputum testing, GeneXpert, chest radiography, and early identification of drug-resistant TB, along with screening of household contacts.

Effective management requires strict adherence to anti-tubercular therapy, regular follow-up, nutritional support, smoking cessation, and monitoring for drug side effects. For resistant cases, individualized regimen and specialist involvement are recommended.

These guidelines highlight early diagnosis, complete treatment, and patient education as key to reducing disease burden and improving outcomes. We appreciate all contributors to this work and reaffirm our commitment to strengthening TB control and respiratory health throughout Pakistan.

Prof. Muhammad Ashraf Jamal
Chairman Guideline Committee
Pakistan Chest Society

Pakistan Chest Society

Guideline Committee

Prof. Muhammad Ashraf Jamal

Chairman, Guidelines Committee
Pakistan Chest Society

Prof. Nisar Ahmed Rao

Professor of Pulmonology
Fazaia Ruth Pfau Medical College & Hospital, Karachi

Prof. Saadia Ashraf

Head of the Pulmonology Department
Khyber Teaching Hospital, MTI, Peshawar

Brig (R) Jamal Ahmad

Head of the Pulmonology Department
Fauji Foundation Hospital Rawalpindi

Prof. Talha Mahmood

Professor & Head of Department (Pulmonology)
Shaikh Zayed Medical Complex, Lahore

Dr. Maqbool A Langove

Associate Professor, Department of Pulmonology
Fatima Jinnah General and Chest Hospital, Quetta

Dr. Kamran Khan Sumalani

Associate Professor, Department of Pulmonology
Jinnah Postgraduate Medical Center, Karachi

Tuberculosis

Guideline Working Group

Prof. Nisar Ahmed Rao

(Chairman working group)
Professor of Pulmonology
Fazaiya Ruth Pfau Medical College & Hospital, Karachi

Dr. Muhammad Saqib Musharaf

Associate Professor of Pulmonology
Gulab Devi Hosp Lahore

Dr. Shahid Salam

Consultant Pulmonologist and MDR Coordinator PTP,
Khyber Pakhtunkhwa

Dr. Nadeem Ahmed

Senior Medical Officer
Ojha Institute of Chest Diseases
Dow University of Health Sciences, Karachi

Dr. Syed Waheed Shah

Consultant pulmonologist
Fatimah Jinnah General and Chest hospital, Quetta

Chapter 01:

Introduction, Facts and Figures, Epidemiology, Natural History & Risk factors of Tuberculosis

Tuberculosis (TB) is one of the oldest diseases known to affect humans. It is an infectious disease caused in the vast majority of cases by Mycobacterium tuberculosis (MTB). The organism was identified by Robert Koch on 24th March 1882. This day is now commemorated as "World TB Day' throughout the world every year.

Burden of disease

According to Global TB report 2025, globally 10.7 million people fell ill with TB (global incidence 131/100,000). Globally 8.3 million Cases were notified which are 77.6%, about 22.4% cases are missing or not notified. TB is the leading cause of deaths among top 10 infectious diseases with 1.23 million deaths in 2024.

Tuberculosis in Pakistan

Tuberculosis is one of the major public health problems in Pakistan. Pakistan has the world's 5th highest number of people falling ill with TB each year among eight high TB burden countries which accounts for 2/3rd global TB burden. The prevalence, incidence, and mortality per 100,000 population per year from TB in Pakistan are 355, 266 and 20 respectively according to national TB program (NTP).

Pakistan had a burden of 669,000 TB cases in 2024. Pakistan's case notified in 2024 are 497700, while missing cases are 26%. Treatment Success rate of TB cases in Pakistan is 95%.

Despite the fact the Pakistan has achieved high Treatment success rates among notified TB cases (more than 90%), low detection rates remain a formidable challenge. Pakistan still misses TB Cases mainly because of access issue, stigma, sub optimal awareness and associated out of pocket burden on patients.

NTP estimates that 51000 Pakistani citizens died from TB in 2024 including 690 TB patients with HIV, the highest number from any infectious disease.

Tuberculosis is the 7th largest cause of lost years of life in Pakistan, behind the major causes of death in infants and children, and ischemic heart disease.

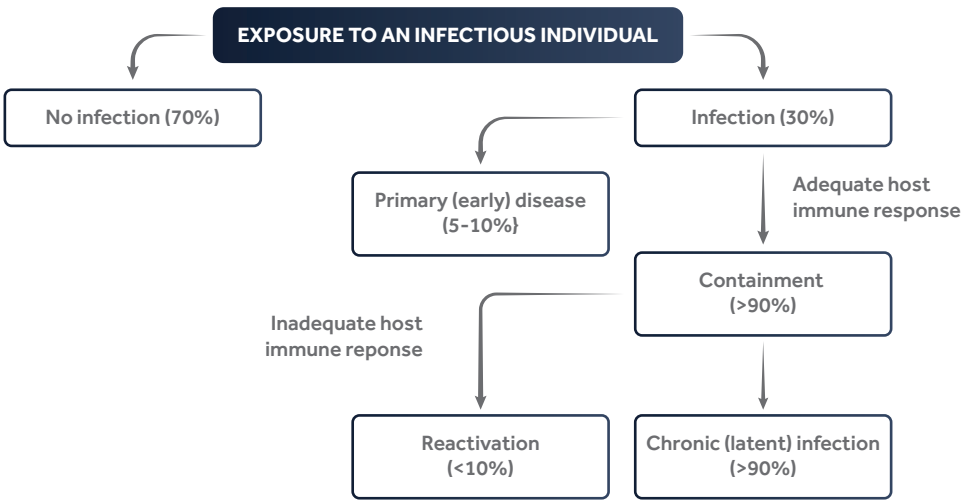
Estimates of Tuberculosis Burden (2023)

Parameter	Numbers	Rate per 100'000 population
Total TB incidence	669'000	266
HIV POS TB incidence	2600	1
MDR/RR-TB	14000	5.4
HIV NEG Mortality	51000	20
HIV POS Mortality	690	0.27

Estimates of proportion of TB cases with MDR/RR-TB (2024)

Natural History of Untreated	1.9 %
Pulmonary Tuberculosis	3.7%

Natural History of Untreated Pulmonary Tuberculosis



Outcome of Untreated Pulmonary Tuberculosis

Tuberculosis is a severe and often deadly disease without treatment. After 5 years without treatment, the outcome of smear-positive pulmonary TB (PTB) in HIV-negative patients will be as follows:

- 50-60% will die (case fatality ratio for untreated TB)
- 20-25% will cure (spontaneous cure)
- 20-25% will still be smear positive TB

Risk Factors for TB

The risk depends on a number of factors including those that lead to a weakened immune system, damaged lungs, or the intensity and duration of exposure:

Host Immune Defenses:

- HIV infection (risk multiplied by 20-40)
- Diabetes mellitus (risk multiplied by 3-5)
- Malnutrition
- Prolonged therapy with corticosteroids (such as prednisolone) and other immune suppressive therapies
- Certain types of cancer (e.g., leukaemia, Hodgkin's lymphoma, or cancer of the head and neck)
- Severe kidney disease
- Alcoholism
- Substance abuse
- Age: Young children (children under 5 have twice the risk and higher risks are observed for those under 6 months); Persons over sixty years have 5 times the risk
- Pregnancy

Conditions that Damage the Lung:

- Tobacco smoking
- Silicosis

Intensity of Exposure (Number of Inhaled Bacilli):

- Contagiousness of the source
- Environment and proximity in which the exposure took place
- Duration of exposure
- Residents and employees of high-risk congregate setting

References:

1. World Health Organization. Global tuberculosis report 2024. Geneva: WHO; 2024.
2. National TB Control Programme (Pakistan). National TB Control Programme – Common Management Unit. Islamabad: Government of Pakistan; 2024.

Chapter 02:

Tuberculosis; Definition, Transmission, Pathogenesis and Disease Forms

Tuberculosis is an infectious bacterial disease caused by Mycobacterium tuberculosis complex which most commonly affects the lungs (app 80%). Mycobacterium tuberculosis is a rod-shaped bacillus that resist alcohol and acid due to its thick lipid wall (acid & alcohol fast). It multiplies more slowly (doubling time 18 hours) that causes disease in weeks or even months to years after infection. It is strictly aerobic bacterium that multiplies better in pulmonary tissue (in particular at the apex, where oxygen concentration is higher) than in the deeper organs.

Transmission and Pathogenesis:
Tuberculosis is transmitted from person to person via droplets from people with the active respiratory disease. Tiny droplets thus create dry rapidly, attach themselves to fine dust particles and smallest of them may remain suspended in the air for several hours. The number of infectious droplets projected into the atmosphere by a patient when coughing (3500) or sneezing (1 million). Only those particles that are less than 10 microns in diameter reach the pulmonary alveoli and result in the infection of individual. A healthy person might be infected by inhaling these tiny particles and developing a primary complex in the lungs. Infection with Mycobacterium tuberculosis, in most healthy people, often causes no symptoms since the person's immune system acts to wall off the bacteria. However, in some people the tuberculosis bacteria will spread from the primary lung lesion to other parts of the body via the blood stream and lymphatics or by direct extension, and in this way may affect any organ.

Approximately 5–10% of individuals with latent tuberculosis infection (LTBI) will develop active TB disease during their lifetime. The risk of progression is highest soon after infection. Studies have shown that 75% of active TB cases in contacts occur within one year of diagnosis of TB in the index case, and 97% within two years.

Disease forms:
Tuberculosis (TB) exists in two main forms: TB infection (latent TB) and TB disease (active TB).

1. TB Infection (Latent TB Infection - LTBI):
The person is infected with Mycobacterium tuberculosis but does not have symptoms and cannot spread the disease.

2. TB Disease (Active TB):
The bacteria are actively multiplying and causing symptoms.

Chapter 03:
Clinical presentation, presumptive identification and Disease classification

Clinical Presentation of Tuberculosis
Clinical symptoms depend on the site involved.

Pulmonary Tuberculosis (PTB)

1. Constitutional Symptoms (Systemic):
Due to body's immune response to Mycobacterium tuberculosis and include:
Fever (low-grade, often in the evening), Night sweats, Weight loss (unintentional, due to chronic inflammation), Fatigue, Loss of appetite.

2. Respiratory Symptoms:
Due to lung involvement and include:
Chronic cough (initially dry, later productive with sputum), Hemoptysis, Chest pain (pleuritic or dull, due to pleural involvement), Shortness of breath (seen in extensive disease or pleural effusion)

3. Physical Examination Findings:
May be normal in early disease, Crackles over the affected lung, localized wheeze in case of endobronchial tuberculosis.

4. Radiological Features (on chest X-ray or CT scan):
Cavitary lesions, Nodular opacities (infiltrates, typically in the apical or posterior segments upper lobes, apical basal segments of lower lobes), miliary shadows (diffuse 1-2 mm nodules in severe cases), fibrosis in advanced disease

5. Risk Factors for Presentation:
Immunosuppression (HIV/AIDS, diabetes, malnutrition), Close contact with an active TB case, Smoking, Poor socioeconomic conditions etc.

Extra pulmonary Tuberculosis (EPTB)
M. tuberculosis can spread from the lungs to other parts of the body via the lymphatic system or bloodstream, leading to extra pulmonary involvement of various organs including the pleura, lymph nodes, meninges, abdomen, joints, bones, genitourinary tract, gastrointestinal tract and skin etc. clinical presentation of extra pulmonary tuberculosis is relevant to the organ involvement while the Constitutional Symptoms like Fever , Night sweats, Weight loss, Fatigue and Loss of appetite are common as in pulmonary tuberculosis.

1. Lymph Node Tuberculosis
It is the most common form of extra pulmonary TB. It is more common in children and HIV-infected patients. It presents with Painless, gradually enlarging lymph nodes (commonly cervical, but also axillary, hilar, mediastinal etc.), the nodes are initially firm and

mobile but may become matted together. Can progress to cold abscess formation (fluctuant, non-tender swelling). Over time, the abscess may rupture, leading to sinus formation with caseous discharge.

Diagnosis: Fine-Needle Aspiration Cytology (FNAC) or Biopsy showing caseating granulomas (hallmark of TB), tissue for Acid-fast bacilli (AFB) staining & AFB culture may be positive. Tissue for Xpert MTB Rif Assay is positive in 50-90% in different studies (higher in caseous or necrotic lymph nodes (~70%–90%), Lower in non-necrotic nodes (~50%–70%).

2. Tuberculous Pleural Effusion

It is the most common cause of pleural effusion in Pakistan. It is usually unilateral, and the fluid is mild to moderate in amount. On chest X-ray, lung involvement is seen in 20% of cases, while on CT scan, it is detected in up to 80% of cases.

TB pleural effusion develops due to:

1. Delayed hypersensitivity reaction – The immune system reacts to mycobacterial antigens, causing pleural inflammation and fluid leakage.

2. Rupture of a sub pleural focus – TB bacilli spread from adjacent lung lesions into the pleural space.

It is presented with fever, pleuritic chest pain, cough (usually dry) and breathlessness (if effusion is large). The diagnosis is confirmed by chest X-ray, pleural fluid examination ±Pleural biopsy.

3. Miliary Tuberculosis:

Miliary tuberculosis is a severe form of tuberculosis that occurs when Mycobacterium tuberculosis spreads through the bloodstream, leading to widespread infection in multiple organs. It is named "miliary" because the tiny TB lesions in the lungs resemble millet seeds on radiological imaging. This condition can affect the lungs, liver, spleen, brain, and other organs. It presents with high grade fever, night sweats, weight loss, and respiratory distress. Miliary TB is a medical emergency requiring prompt diagnosis (via sputum/bronchial wash for MTB GeneXpert, AFB smear & culture, imaging, and biopsy) and treatment.

S.No	EPTB site	Specific clinical manifestation
1	Abdominal TB (Intestine)	Abdominal pain, intestinal obstruction, mass in right iliac fossa
2	Abdominal TB (Peritoneum)	Abdominal pain, ascites
3	Spine TB (POTT's disease)	Chronic persistent backache, restricted spinal movement, neurological deficit (weakness, numbness, paralysis in severe cases)
4	Articular (Joint) TB	Chronic pain and joint swelling

5	TB meningitis	Fever, severe headache, vomiting, signs of meningeal irritation like neck stiffness, Kernig's sign, confusion, seizure, coma
6	Renal TB	Urinary frequency, dysuria, hematuria, flank pain
7	Genital TB	Men: Epididymitis, testicular swelling Female: Pelvic pain, irregular menstruation, infertility

Identifying Presumptive Pulmonary TB case:
Presumptive pulmonary tuberculosis refers to a person with any of the signs and symptoms suggestive of tuberculosis or abnormality in chest radiograph.

A presumptive TB is typically identified as follows:

Signs and symptoms

- Persistent Cough for 2 weeks or more
- Persistent Cough of any duration with one or more associated TB symptoms Fever, Night Sweats, Weight loss, Loss of appetite, Fatigue, Chest pain, Hemoptysis.

For people living with HIV, WHO recommends four primary symptoms screening (W4SS) for TB including cough, fever, weight loss or night sweats.

Chest X-ray
Patients with abnormal shadows on chest X-ray consistent with TB like cavitation, infiltration, effusion, hilar lymph adenopathy.

Definitions:
These definitions are important for registration and programmatic management.

Presumptive Tuberculosis: Any person who presents with symptoms or signs suggestive of Tuberculosis (previously known as TB suspect).

Case of Tuberculosis: A definite case of TB (defined below) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of anti-TB treatment.

Note: Trial for TB treatment should not be considered as a method for diagnosis.

Bacteriologically Confirmed TB Case: is one from whom a biological specimen is positive by smear microscopy, culture, Xpert MTB/RIF assays (GeneXpert) or molecular line probe assay. All such cases should be notified, regardless of whether TB treatment has started.

Clinically Diagnosed TB Case: is one who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition

includes cases diagnosed on the basis of X-¬-ray abnormalities or suggestive histology and extra pulmonary cases without laboratory confirmation.

Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Disease Classification

Tuberculosis is classified on the basis of criterion defined in the table.

Criteria	Classification/Type	
Anatomical site	Pulmonary	Extra-pulmonary
Severity	Non-severe	Severe
Diagnostic tool	Bacteriologically positive (microscopy/culture/WRD)	Clinically diagnosed (clinical history/CXR)
Drug resistance pattern	Drug susceptible	Drug resistance
HIV status	HIV-positive	HIV-negative
History of ATT drug intake	New	Previously treated
Reporting	All incidents (N+R+UK)	Total / prevalent (N+R+ previously treated)
Treatment outcome	Successful	Un-successful

WRD: WHO recommended diagnostic like GeneXpert N: New R: Relapse UK: Unknown

Definition as per Disease Classification

Pulmonary Tuberculosis (PTB): This refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs.

Extra Pulmonary Tuberculosis (EPTB): This refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs e.g. pleura, lymph nodes, abdomen, genitourinary tract etc.

Severe or Extensive Tuberculosis Disease: This refers to bilateral cavitary disease or extensive parenchymal damage or Miliary TB on chest radiography.

In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on CXR. TB meningitis and extra pulmonary forms of disease in children other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are severe.

Non-Severe Tuberculosis: This refers to Intrathoracic lymph node TB without airway obstruction, uncomplicated TB pleural effusion, paucibacillary, non-cavitary lung disease confined to one lobe of the lungs.

Drug-Susceptible TB (DS-TB): Drug-susceptible TB (DS-TB) refers to tuberculosis caused by strains of Mycobacterium tuberculosis that are not resistant to the standard first-line anti-TB drugs. Under programmatic conditions, this includes individuals with TB disease in whom drug susceptibility testing (DST) was not performed or whose MTB GeneXpert result indicates no rifampicin resisttance.

First-Line TB Drugs: These are the drugs used to treat a person with drug-susceptible TB disease. These include Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E).

Drug-Resistant TB (DR-TB): A person with TB disease who is infected with a strain of Mycobacterium tuberculosis complex that is resistant to one or more of the anti-TB medicines tested.

Second-Line TB Drugs: These are the drugs used to treat a person with drug-resistant TB disease.

HIV-Positive: A person with TB disease who has documented positive HIV test results before, at the time of TB diagnosis, or during the course of TB treatment.

HIV-Negative: A person with TB disease who has a documented negative HIV test result obtained at the time of TB diagnosis.

HIV Status Unknown: A person with TB disease who has no documented HIV test result and no evidence of receiving HIV treatment.

Classification Based on Previous Tuberculosis Treatment

New Case: A person with TB disease who has never been treated for TB or has taken TB drugs for less than 1 month.

Recurrent Case: A person with TB disease who has previously been treated for TB, was declared cured or treatment completed at the end of their most recent course of TB treatment and is now diagnosed with a new episode of TB.

Re-registered Case: A person with TB disease who has been notified previously as a TB case, who started TB treatment and took TB drugs for at least 1 month but who was not declared cured or treatment completed, and is now being started on a new course of TB treatment.

Unknown Previous Treatment History: A person with TB disease who has no documented history of TB treatment.

New Episode: A person with TB disease who has either a new, recurrent or unknown previous TB treatment history (i.e. any case apart from a re-registered case).

Previously Treated Case: A person with TB disease who is either a recurrent or a re-registered case.

Classification Based on Treatment Outcome

Cured: A patient registered as smear-positive, has completed the duration of treatment, and becomes sputum smear negative at the end of treatment and on at least one previous occasion.

Treatment Completed: A person with TB disease who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure.

Treatment Successful: A person with TB disease who was either cured or who completed treatment as defined above.

Treatment Failed: A sputum smears positive patient who remains or becomes sputum smear positive at month five or later.

Died: A person with TB disease who died for any reason before starting (for case outcomes), or during the course of, treatment (for both case and treatment outcomes).

Lost To Follow- Up: A person with TB disease who did not start treatment (for case outcomes) or whose treatment was interrupted for two consecutive months or more (for both case and treatment outcomes).

Not Evaluated: A person with TB disease to whom no treatment outcome was assigned, excluding those lost to follow up.

All TB cases should be notified to public health authorities, regardless of whether TB treatment was started. People with TB who died or were lost to follow up before TB treatment started should also be notified to public health authorities; this is because they are important from the perspective of both surveillance and public health (they may have contacts that require tracing and follow up).

Chapter 04:
TB Case Finding and TB Screening

TB case finding involves identifying presumptive TB, either by clinical signs and symptoms and/or chest X-ray, followed by the diagnosis of active TB disease through bacteriological testing or clinical diagnosis. The term is sometimes used synonymously with "systematic screening". It is referred to as "intensified case-finding" when conducted in health-care facilities and as "enhanced case-finding" when conducted in communities.

Rationale, Aim and Objective of Active Case findings
Tuberculosis is a major yet preventable airborne infectious disease which has high global incidence and prevalence. The aim of screening (or active TB case finding) is to detect TB disease early in order to minimize avoidable delays in diagnosis and initiation of treatment, thereby reducing the risk of unfavorable treatment outcomes.

The primary objectives of Active case finding are to augment standard TB care practices at individual and community level. The first objective is to ensure that TB disease is detected early, and treatment is initiated promptly So that transmission of disease is prevented which in turn reduces the community-level prevalence of TB disease.

Passive TB Case Finding
It is the most common approach to identify TB among individuals who seek care in a health care setting. Patients present with specific signs and symptoms, and a health care worker assesses these symptoms and/or chest X-rays to identify presumptive TB. In PLHIV suspected of pulmonary tuberculosis, WHO recommends the four-symptom screen (W4SS) for TB: cough, fever, weight loss, or night sweats. It is called the patient-initiated pathway to TB diagnosis and relies on patients seeking care and on health systems to respond quickly and appropriately.

Active Case Finding
Detecting TB among people who do not present to health facilities causing case-detection gaps, particularly in certain vulnerable populations, and the persistence of diagnostic delays and resulting continued transmission in the community, indicate the need for a more active approach to early detection of TB. This justifies systematic screening of selected risk groups and populations for TB disease. It is also called Provider-initiated TB screening pathway; this approach can target people at different stages of TB.

Systematic Screening for TB
Systematic screening is defined as "The systematic identification of people at risk for TB disease, in a pre-determined target group, who do not seek health care. The WHO End TB Strategy includes systematic screening for TB disease in high¬ risk groups as a central component of its first pillar.

Recommended Risk Group For Systematic Screening For Tb

Target group	Recommendation
General population where prevalence is 0.5% or high	Conditional
People with risk group (urban poor community, immigrants, refugees and IDPs.	Conditional
People living with HIV	Strong
Household contact of individuals with TB	Strong
People living in prisons	Strong
Miners and others exposed to silica dust	Strong
People attending healthcare services have clinical risk of TB (when prevalence is 100/100,000 or high)	Conditional

Principles of TB Screening

Screening program must include an appropriate pathway for screening, diagnostic confirmation, treatment and care and further management. The following six key principles should be considered in planning a TB screening initiative:

Principle 1: TB screening should always be done with the intention of following up with appropriate medical care.

Principle 2: Screening should reach the people at greatest risk of developing TB disease.

Principle 3: TB screening should follow established ethical principles for screening including obtaining voluntary informed consent.

Principle 4: The choice of algorithm for screening and diagnosis should be based on its accuracy for target risk group, as well as the availability.

Principle 5: TB screening should be synergized with the delivery of other health and social services.

Principle 6: Screening program should be regularly monitored.

TB Screening Tools

TB screening tools are designed to identify people with a higher probability of having TB disease. They are not intended to provide a definitive diagnosis. Screening tests should distinguish between people with a high likelihood of having TB disease from those who are unlikely to have TB. It should include symptom screening for clinical features associated with pulmonary TB and screening with CXR.

Symptom Screening

Symptom screening is feasible, easy to implement and low-cost. It is highly acceptable and is a usual part of the clinical assessment of people under care. Symptom screening,

particularly for cough, has the added advantage of detecting people with TB who are most likely to transmit disease.

CXR Screening

CXR is a rapid imaging technique for identifying lung abnormalities. CXR is a good screening tool for pulmonary TB because of its high estimated accuracy for detecting TB disease, especially before the onset of symptoms.

Molecular WHO-Recommended Rapid Diagnostics For Screening (mWRDs) are rapid, sensitive molecular tests for detecting TB. These are also recommended for screening for TB disease. The mWRDs that can be used for screening are Xpert® MTB/RIF and Xpert MTB/RIF Ultra, loop-mediated isothermal amplification (LAMP).

Tests of TB Infection

The tuberculin skin test, like the Mantoux test and interferon-g release assays should not be used in screening of TB disease. These tests cannot distinguish TB infection from TB disease and cannot predict who will progress to TB disease.

Recommended Algorithms for Screening in Pakistan

For screening of high-risk groups in Pakistan, it is recommended that the parallel screening with symptoms (Prolonged cough) and CXR should be used and those screened positive should be tested using WHO-recommended rapid test for diagnosis of TB disease. Out-of-household exposure is as likely to result in transmission as household exposure; however, contacts in settings like schools, workplaces, or hospitals are difficult to identify. Close exposure, such as sharing a living or working space, is generally easily identified and quantified, whereas casual exposure, such as on public transport or in social situations, may be unidentifiable.

It is recommended that contact investigation of all Bacteriologically confirmed pulmonary TB patients should be conducted for household members and close contacts.

Screening Child Contacts Of Patients With TB

Any child < 15 years who has had close contact with someone with TB disease should be screened for TB with a symptom screen and/or CXR as part of active contact tracing. Symptoms that should be used to screen for TB in children are cough, fever and poor weight gain (or weight loss) reduced playfulness or lethargy.

Adults And Adolescents Living With HIV

People living with HIV be systematically screened for TB disease. Screening with the WHO four-symptom screen (W4SS) is recommended for all people living with HIV at every encounter with a health-care worker, both to detect prevalent TB disease and to rule it out before initiation of TPT (Tuberculosis Preventive Treatment).

Mine Workers

A CXR-based screening approach, together with screening for symptoms of TB and lung disease, is also preferred for miners exposed to silica, given their high risk of lung disease

(including TB) and lung damage from silicosis.

Prisoners

Given the high risk of transmission in this group, a highly sensitive algorithm beginning with CXR is preferred.

People With Clinical Risk Factors

In Pakistan, where the general TB prevalence is > 100/100 000, TB screening may be conducted among people with TB risk factors who are seeking health care for any medical reason or among those who are in health care. Access to radiography is more likely in a health facility. This can maximize screening sensitivity. Symptom screening is also valuable for immediate decisions on triage and infection control.

General Population And Communities With Structural Risk Factors

For screening in the community, in populations with structural risk factors for TB and/or in the general population when the TB prevalence is 0.5%, a highly sensitive screening algorithm is recommended. Screening for symptoms, although is much easier but is less sensitive and specific

Diagnostic accuracy of symptoms, CXR and mWRDs for screening for TB disease among HIV-negative individuals

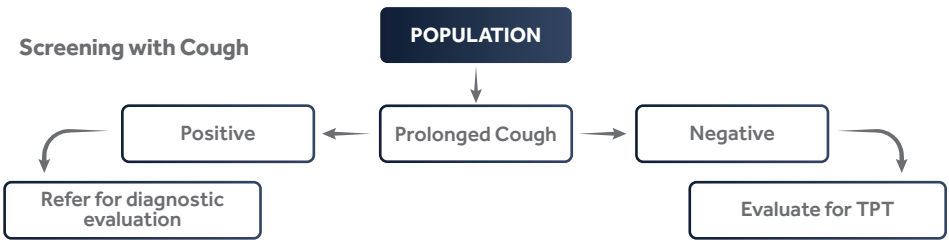
Screening test	Specificity (%)	Specificity (%)
Prolonged cough (≥ 2 weeks)	42	94
Any cough	51	88
Any TB symptoms (cough, hemoptysis, fever, night sweats, weight loss)	71	64
CXR (any abnormality)	94	89
CXR (abnormality suggestive of TB)	85	96
mWRDs (adults at high risk)	69	99

Algorithms For Screening

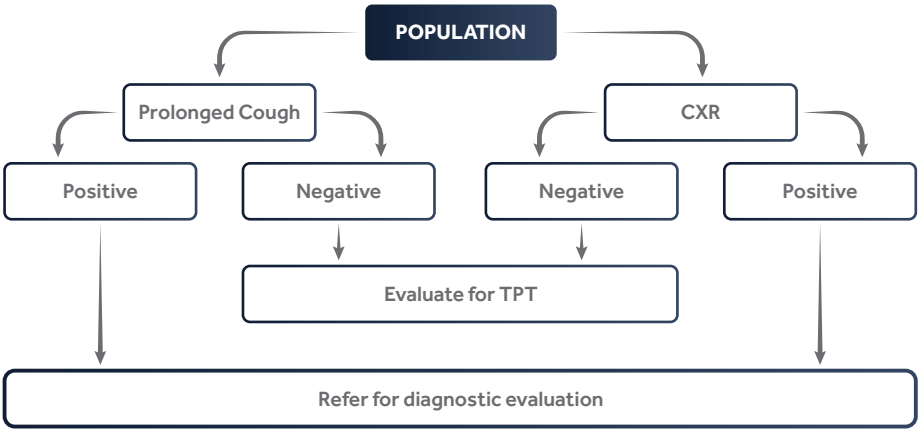
An algorithm for systematic TB screening should combine one or several screening tests and a separate diagnostic evaluation for TB disease, as recommended by WHO).

A Negative diagnostic test result may be followed up by further clinical evaluation if clinical suspicion of TB is still high. A positive diagnostic test result might have to be re-confirmed with further testing and clinical evaluation if the positive predictive value of the test result is low.

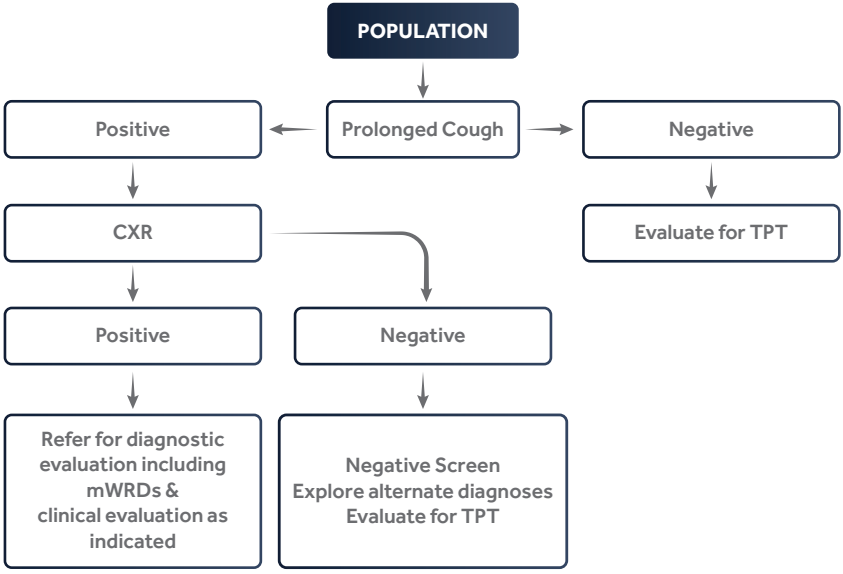
Screening with Cough



Parallel Screening With Cough And Cxr



Sequential Positive Serial Screening With Cough And CXR



References:

1. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 2: Screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021. ISBN: 978-92-4-002267-6.
2. World Health Organization. WHO operational handbook on tuberculosis: Module 2: Screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021. ISBN: 978-92-4-002261-4.
3. Rapid communication on systematic screening for tuberculosis. Geneva: World Health Organization; 2020.
4. National Tuberculosis Guidelines Pakistan (Revised) 2024.

Chapter 05:
Diagnosis of Tuberculosis

Tuberculosis (TB) diagnosis involves a combination of clinical evaluation, imaging, and laboratory tests to distinguish between latent TB infection (LTBI) and active TB disease. Active TB diagnosis requires confirmation of the presence of Mycobacterium tuberculosis (MTB).

Test Name/Method	Purpose	Specimen/Process	Key Features
Medical History & Physical Exam			
Medical history + physical exam	Initial clinical screening, risk factors		Essential but non-specific; cannot rule in/out TB by itself
Latent TB Infection (LTBI)			
Tuberculin Skin Test (TST) / Mantoux test	To detect an immune response to MTB (exposure). Cannot distinguish between LTBI and active disease.	Intradermal injection of purified protein derivative (PPD); induration size measured at 48-72 hours.	Low specificity due to cross-reactivity with BCG vaccination and non-tuberculous mycobacteria. Requires two visits.
Interferon-Gamma Release Assays (IGRAs) (e.g., QuantiFERON-TB Gold, T-SPOT.TB)	To detect an immune response to MTB (exposure). Cannot distinguish between LTBI and active disease.	Blood sample incubated with specific MTB antigens (ESAT-6, CFP-10); measures IFN- release.	**Higher specificity** than TST as they are less affected by BCG vaccination. Requires only one visit.
Serological Antibody Tests (e.g., MycoDot, TB-IgG ELISA)	An immunochromatographic assay (e.g., dot-blot format) that detects IgG and IgM antibodies against M. tuberculosis antigens, most commonly **Lipoarabinomannan (LAM).**	Specimen: Serum Historically used to aid in the diagnosis of active TB, especially in smear-negative or EPTB cases.	Simple, rapid (20 minutes), requires no specialized equipment. However, WHO strongly recommends against the use of existing commercial serological tests due to low and variable sensitivity and specificity.
Active TB Disease (Microbiological – Microscopy)			
Acid-Fast Bacilli (AFB) Smear Microscopy (e.g., Ziehl-Neelsen, Fluorescent LED	Rapid initial detection of mycobacteria (Acid-Fast Bacilli).	Sputum or other clinical specimen (e.g., CSF, biopsy) is stained and examined under a	**Fast and inexpensive** but has **low sensitivity** (requires 5000 bacilli/mL) and cannot

Microscopy)		microscope.	differentiate M. tuberculosis from other mycobacteria.
Active TB Disease (Microbiological – Culture)			
Principle			
Culture (Solid or Liquid media)	**Gold Standard** for confirming active TB diagnosis and for Drug Susceptibility Testing (DST).	Sputum or other clinical specimen inoculated onto media to allow growth of MTB.	**Most sensitive** test, detects lower bacterial load. Allows for phenotypic DST. Liquid culture is faster (weeks) than solid culture (weeks).
Culture Types, Purpose, Specimen, Key Principle, Advantages, Disadvantages and Limitations			
Löwenstein–Jensen (LJ) medium	Detects viable Mycobacterium tuberculosis complex (MTBC) and other mycobacteria through visible colony growth on solid egg-based medium	Sputum, BAL, gastric aspirate, pleural fluid concentrate, lymph node or tissue biopsy, CSF, urine	**Principle:** Growth on solid medium with malachite green (inhibits contaminants). **Incubation:** 35–37 °C; colonies visible in 3–8 weeks. **Appearance:** Rough, buff, non-pigmented colonies ("Rough, Tough, Buff"). **Advantages:** Inexpensive; distinguishes mixed colonies; supports contamination check. **Limitations:** Slow growth; lower sensitivity vs liquid culture; not ideal for rapid DST. **Use:** Recommended to run alongside liquid system to confirm growth and avoid false positives.

Middlebrook 7H10 / 7H11 agar	**Detects M. tuberculosis and nontuberculous mycobacteria (NTM)**	Sputum, BAL, tissue homogenates	**Principle:** Transparent agar base allows early detection of colonies under magnification. Incubation: 2–4 weeks typical. **Advantages:** Faster than LJ; easier to visualise colonies; supports DST and identification. **Limitations:** Higher contamination risk; requires CO_2 incubator; costlier. **Use:** Preferred in research and reference labs for species differentiation and drug testing.
BACTEC MGIT 960 (Mycobacteria Growth Indicator Tube)	**Detects growth of M. tuberculosis complex and M. avium complex via oxygen** consumption (fluorescence quenching)	Sputum, BAL, gastric aspirate, pleural fluid, CSF, lymph node, tissue, bone marrow	**Principle:** Fluorescent indicator quenched by O_2 → growth reduces O_2 → fluorescence increases. Automated detection every 60 min. **Media:** Middlebrook 7H9 broth with OADC enrichment and PANTA (antibiotics). **Turnaround:** 7–14 days average for positives; negatives declared after 42 days. **Advantages:** Most sensitive, fastest conventional culture; automated reading; suitable for first line and second-line DST; can

			quantify growth rate/time-to-detection (TTD). **Limitations:** Needs continuous power supply and biosafety; higher contamination rate (~8–12%) than LJ. **Use:** WHO-recommended standard for reference and national TB labs. **Principle:** Uses
BACTEC 460 (Radiometric system) (obsolete in many centers)	Detects radiolabeled CO_2 from metabolized substrate by growing mycobacteria	Sputum, tissue, sterile fluids	^{14}C-labeled palmitic acid; growth detected radiometrically. **Advantages:** Rapid (mean 10–14 days). **Limitations:** Uses radioactive material → costly waste handling → replaced by MGIT. **Use:** Historical relevance; largely phased out.
Microscopic Observation of Drug Susceptibility (MODS) assay	Detects M. tuberculosis via cord-like microscopic growth in liquid media (Middlebrook 7H9 + antibiotics)	Sputum, BAL, CSF	**Principle:** Visual microscopic detection of characteristic serpentine cords. **Turnaround:** 5–10 days. **Advantages:** Rapid, low-cost; detects growth and DST simultaneously. **Limitations:** Requires microscopy skill; higher contamination; not fully automated. **Use:** Endorsed by WHO as low-cost option in

			resource-limited labs.
BACT/ALERT 3D Myco System (bioMérieux)	Detects Mycobacterium spp. via CO_2 production monitored by colorimetric sensor	Blood, sterile body fluids, tissues	**Principle:** CO_2 production → pH indicator change optical detection. **Turnaround:** 10–20 days. **Advantages:** Automated, continuous monitoring; suitable for disseminated TB (esp. HIV+). **Limitations:** Less sensitive for respiratory specimen's vs MGIT; costlier.
VersaTREK Myco System (Thermo Fisher)	Detects M. tuberculosis via gas pressure changes in headspace (aerobic/anaerobic growth detection)	Blood, sterile fluids	**Principle:** Growth produces gas, changing headspace pressure; automated detection. **Advantages:** No radioactive waste; broad organism range. **Limitations:** Slightly slower than MGIT; limited field validation for TB.
Myco/F Lytic system (Becton Dickinson)	Detects Mycobacteria from sterile fluids (esp. blood, CSF) using lytic medium and CO_2 production	Blood, sterile fluids	**Principle:** Lyses blood cells → releases intracellular organisms → grows in broth. **Turnaround:** 2–4 weeks. **Advantages:** High yield in disseminated or extrapulmonary TB. **Limitations:** Not ideal for sputum; high contamination risk if used for respiratory

			specimens.
FASTPlaque TB Assay (Phage-based detection)	Mycobacterial growth by bacteriophage infection	Sputum, BAL, other body fluids	**Principle:** Bacteriophages infect M. tuberculosis; viable bacilli protect phage DNA → detectable plaque formation. **Advantages:** Detects viable bacilli within 1–2 days. **Limitations:** Moderate sensitivity; not WHO-recommended as routine diagnostic; needs viable organisms.
HPLC (High-Performance Liquid Chromatography)	Mycolic acid patterns for species identification	Culture isolates	**Principle:** Analyzes mycolic acid profiles unique to each mycobacterial species. **Advantages:** Differentiates MTB from NTM. **Limitations:** Requires pure culture and specialized equipment; slow.
Mass Spectrometry (MALDI-TOF MS)	Protein fingerprint of M. tuberculosis and NTM	Culture isolates	**Principle:** Laser desorption ionization to analyze protein spectra. **Advantages:** Rapid species identification within minutes once cultured. **Limitations:** Requires cultured organisms; cannot directly test sputum.
Active TB Disease (Other Molecular Genetic Tests			
Principle			
Nucleic Acid	Rapid detection of MTB	Sputum, other body	**Rapid results** (hours or

Amplification Tests (NAATs)	DNA and drug resistance (e.g., Rifampicin resistance).	fluids, or processed tissue loaded into a cartridge/device.	less). WHO-endorsed for initial diagnosis.
Tests and their Utility			
Xpert MTB/RIF	MTBC + rpoB (RIF-R)	Sputum; also, CSF for TB meningitis; selected EPTB fluids/tissues	Initial test of choice per WHO; wide evidence base.
Xpert Ultra	MTBC (lower LOD than Xpert) + rpoB Ultra has higher sensitivity but lower specificity than Xpert.	Sputum; also, CSF for TB meningitis; selected EPTB fluids/tissues Xpert	Higher sensitivity (especially paucibacillary); "trace" results need clinical context.
Xpert MTB/XDR	INH (katG/inhA), FQs (gyrA/B), AMK/KAN/CAP (rrs/eis), ETH (inhA)	Reflex on Xpert-positive specimens,	Expands rapid DST beyond RIF.
Truenat MTB / MTB Plus / MTB-RIF Dx	Truenat: nrdZ gene Truenat Plus: nrdZ + MPT64 genes Truenat MTB-RIF: rpoB gene	extrapulmonary fluids	**Principle:** Chip-based micro-PCR platform (battery-operated). **Advantages:** Portable, Battery-operated, faster than culture, RIF resistance detection. **Limitations:** Limited by supply/logistics; primarily used in India.
Line Probe Assays (LPAs) (e.g., Genotype MTBDRplus, MTBDRsl)	MTB DNA & resistance mutations (rpoB, katG, inhA, gyrA/B, rrs) To rapidly detect drug resistance (MDR/XDR-TB) to firstand second-line drugs.	Biopsy tissue, pus, aspirate, positive culture Amplified DNA from culture or direct specimen is hybridized to a membrane strip.	**Principle:** DNA strip hybridization; detects genotypic resistance to first-/second-line drugs. **Advantages:** 1–2 days turnaround; detects MDR-TB. **Limitations:** Requires sufficient bacillary load; costly.
			Principle: Isothermal DNA amplification producing turbidity/fluorescence; no need for PCR

TB-LAMP (Loop-Mediated Isothermal Amplification)	MTB DNA (amplification without thermal cycling)	Sputum, BAL, pleural fluid	machine. **Advantages:** Fast (~1 hour), simple, suitable for field use. **Limitations:** Slightly lower sensitivity than Xpert Ultra; still limited availability. **WHO Status:** Endorsed as an alternative rapid molecular test in resource-limited settings.
BDQ/CFZ Resistance Testing & Interpretation			
Method available	Role	Specimen (examples)	Notes — principle, advantages, disadvantages/ limitations
1.Whole-Genome Sequencing (WGS)	Detects all known mutations linked to BDQ/CFZ resistance (notably Rv0678, atpE; also, pepQ, mmpL5/mmpS5). Use a WHO Catalogue (2023) to translate variants probability of resistance for clinical decisions.	DNA from culture isolates (preferred); some labs perform direct WGS from high-bacillary sputum	**Principle:** Shotgun sequencing variant calling catalogue-based interpretation. **Advantages:** Comprehensive; detects mixed populations; supports outbreak/lineage data. **Limitations:** Infrastructure/cost; turnaround of days; genotype–phenotype correlation is imperfect for Rv0678 (many variants show low/variable MIC shifts). atpE variants are rarer but usually high-level BDQ resistance
			Principle: PCR amplifies target genes sequence

2.Targeted sequencing (Sanger/amplicon or targeted NGS) of Rv0678 ± atpE (± pepQ, mmpL5/mmpS5)	Focused detection of driver mutations causing BDQ/CFZ resistance/cross-resistance. Use WHO Catalogue to assign resistance probability.	**Culture isolates**; selected high-bacillary clinical specimens (direct PCR)	interpret via WHO Catalogue. **Advantages:** Faster/cheaper than WGS; actionable for Rv0678 cross-resistance to BDQ/CFZ via MmpS5–MmpL5 efflux upregulation. **Limitations:** Misses off-target mechanisms; many Rv0678 variants confer low-level/variable MIC; clinical correlation needed.
3.Phenotypic DST (MIC testing) — e.g., broth microdilution or MGIT MIC for BDQ/CFZ	Confirms growth at critical concentrations (the reference for clinical resistance). Used to validate genotypic calls or resolve variants of uncertain significance (VUS).	Culture isolates only (viable MTB required)	**Principle:** Measure growth inhibition across dilutions. **Advantages:** Direct phenotype; resolves ambiguous Rv0678 calls. **Limitations:** Specialized methods/QA; cut-offs evolving; slower TAT; biosafety required. atpE mutations typically yield high MICs; Rv0678 often low-to-moderate MIC increase with CFZ cross-resistance.
4.Commercial LPAs specifically for BDQ/CFZ	Limited/variable availability; many programs rely on WGS/targeted sequencing instead.	N/A	**Principle:** Probe hybridization for predefined mutations. **Advantages:** Rapid if available. **Limitations:** Coverage

			is limited vs sequencing; not universally endorsed/available; may miss Rv0678 diversity. (Programs generally use WGS/targeted sequencing + MIC.)
Active TB Disease (Other Molecular Genetic Tests)			
RNA Transcriptomic Signatures (e.g., 3-gene or 16-gene signatures)	Measures the expression levels of a panel of host genes (RNA) in whole blood, which are altered in response to active TB infection.	**Differentiate Active TB from other diseases and Latent TB Infection;** potential for predicting progression to active disease or monitoring treatment response.	**Emerging field.** Signatures like the 3-gene set (GBP5, DUSP3, KLF2) show promise for high diagnostic accuracy in differentiating active TB. Not yet routine clinical practice.
PCR for specific genes (IS6110, MPB64, 85B, etc.)	MTB DNA / species identification	Tissue, CSF, biopsy, pleural fluid	**Principle:** Amplification of TB-specific genomic targets (IS6110 most common). **Advantages:** Rapid, specific, works on non-sputum specimens. **Limitations:** Risk of contamination; does not differentiate live vs dead bacilli.
Line Probe Assay (Hain Genotype MTBDRplus / MTBDRsl)	Genotypic mutations linked to drug resistance	Smear-positive sputum, culture isolates	**Principle:** DNA strip hybridization detecting rpoB, katG, inhA, gyrA/B, rrs mutations. **Advantages:** Rapid DST within 1–2 days. **Limitations:** Requires molecular lab; only detects known mutations.

Whole Genome Sequencing (WGS)	Comprehensive genomic resistance and lineage typing	Culture isolate, DNA extract	Principle: Sequencing full MTB genome for drug resistance prediction, strain typing, epidemiology. Advantages: Detects known & novel resistance mutations; high accuracy. Limitations: Expensive, not routine; requires high-end lab infrastructure.
Imaging in TB			
Chest X-Ray (CXR)	Structural and parenchymal abnormalities due to pulmonary TB (both active and healed lesions)	Thoracic cavity – lungs, pleura, mediastinum	Principle: Uses ionizing radiation to produce a 2D image of thoracic structures. **Typical findings (Active TB):** Upper lobe infiltrates, cavitations, patchy consolidations, nodular opacities, miliary pattern, pleural effusion. **Healed/inactive TB:** Fibrosis, calcified granulomas (Ghon focus), pleural thickening, volume loss. **Utility:** Initial screening test for all TB suspects; supports diagnosis when microbiological confirmation pending. **Advantages:** Quick, inexpensive, widely available, essential for follow-up. **Limitations:**
a	a		Non-specific; 15% may

			have normal CXR, cannot differentiate TB from other pneumonias, malignancies, or sarcoidosis. **Interpretation:** Radiographic response lags behind microbiologic clearance — always correlate clinically and bacteriologically.
Computed Tomography (CT Chest / HRCT)	Detailed cross-sectional and volumetric detection of parenchymal, pleural, and mediastinal involvement	Lungs, pleura, mediastinum, lymph nodes	**Principle:** Rotating X-ray source with computer-generated 3D reconstruction. **Key findings:** Tree-in-bud nodulesendobronchial spread), centrilobular nodules, cavities with thick/irregular walls, necrotic lymph nodes, bronchiectasis, miliary nodules. **Advantages:** Detects early or occult disease not visible on X-ray; differentiates active vs fibrotic lesions; guides intervention (biopsy, aspiration). **Limitations:** Radiation dose higher; costlier; requires radiologist expertise. **Utility in extrapulmonary TB:** Detects mediastinal lymphadenopathy, pericardial effusion,

			spinal (Pott's) disease. **Contrast CT:** Defines pleural thickening, empyema, pericardial TB. **Findings:** Lymph nodes
CT Abdomen / Pelvis	Extrapulmonary TB: hepatic, renal, adrenal, intestinal, or peritoneal TB	Abdomen, pelvis, retroperitoneal nodes	with central necrosis, thickened bowel loops, omental caking, ascites with high density ("wet type" peritoneal TB). **Use:** Staging, biopsy guidance, differential diagnosis with malignancy
Ultrasound (USG)	Fluid collections, organomegaly, abscesses, and lymphadenopathy due to extrapulmonary TBa	Pleural, pericardial, peritoneal, hepatic, renal, lymph nodes	**Principle:** High-frequency sound waves reflected from tissue interfaces. **Findings:** Anechoic or septated pleural effusions, pericardial effusions, hepatic/splenic hypoechoic lesions ("microabscesses"), mesenteric nodes, ascites with fine internal echoes. **Utility:** First line in pleural, pericardial, or abdominal TB; guides diagnostic estimation and aspiration. **Advantages:** Portable, non-invasive, radiation-free; ideal for children and pregnancy. **Limitations:** Operator-dependent; cannot detect

			parenchymal pulmonary lesions hidden by air.
Ultrasound Thorax (POCUS)	Pleural effusions, consolidation near pleural surface	Pleural cavity	**Findings:** Hypoechoic pleural fluid, fibrinous septations, visceral pleural thickening. **Use:** Guides pleural tap and biopsy; monitors treatment of empyema/TB effusion.
MRI (Magnetic Resonance Imaging)	Soft-tissue detail in extrapulmonary TB – CNS, spine, musculoskeletal, genitourinary	Brain, spine, joints, abdomen, pelvis	**Principle:** Magnetic field & radiofrequency signals generate multiplanar images. **Findings:** Ring-enhancing tuberculomas, meningeal enhancement (TB meningitis), vertebral destruction (Pott's spine), epidural abscess. **Advantages:** No radiation; superior for CNS, bone marrow, and soft tissue TB. **Limitations:** Expensive, limited availability, longer scan time.
PET-CT (Fluorodeoxyglucose-FDG)	Metabolic activity in lesions, differentiates active TB vs inactive or neoplastic lesions	Whole body imaging	**Principle:** FDG uptake correlates with inflammation; active TB lesions show high FDG activity. **Advantages:** Detects occult foci, assesses treatment response, identifies relapse. **Limitations:** Non-specific (false positives in

			malignancy/inflammation); high cost. **Use:** Research, complex or disseminated TB, monitoring response in MDR-TB.
Echocardiography (TTE / TEE)	Pericardial TB manifestations	Pericardium, myocardium	**Findings:** Pericardial effusion, thickening, fibrinous strands, "constrictive pericarditis" pattern. **Utility:** Diagnostic and therapeutic guidance (pericardiocentesis).
Active TB Disease (Molecular Genetic Tests)			
Lipoarabinomannan (LAM) Assay (e.g., Alere Determine TB-LAM Ag)	Rapid detection of LAM antigen in urine, primarily for HIV-positive people with low CD4 counts.	Urine sample.	Point-of-care test particularly useful in immunocompromised patients (HIV-positive with CD4 count cells/L) who may be smear-negative.
Urinary Lipoarabinomannan (LAM) Antigen – FujiLAM (advanced version)	LAM antigen (mycobacterial cell wall glycolipid)	Urine	**Principle:** Immunochromatographic detection of LAM antigen. **Advantages:** High sensitivity in HIV-positive, low CD4 cases; point-of-care. **Limitations:** Low sensitivity in HIV-negative adults; used as adjunct test. **WHO 2023:** FujiLAM recommended hospitalized HIV-positive adults with CD4 <200.
			Simple, rapid, and cost-effective adjunct

Adenosine Deaminase (ADA)	An enzyme produced by lymphocytes (T-cells). High levels indicate a strong cell-mediated immune response, often in fluid effusions.	**Diagnosis of Tuberculous Effusions** (e.g., Pleural, Peritoneal, Meningeal). A fluid ADA level >40 IU/L strongly suggests TB, especially in high-prevalence settings, but is not definitive	test. High negative predictive value (low ADA virtually excludes TB). **ADA-2 isoenzyme** measurement can increase specificity by primarily reflecting T-cell activity. **False positive** in empyema, malignancy, RA, Lymphoma, SLE, Leukemia (T-cell), Fungal or Viral Infections (e.g., Histoplasmosis, Parvovirus B19, CMV, EBV), Chylothorax, HIV-associated lymphocytic effusions (non-TB), Sarcoidosis (rare), and Parasitic infections (e.g., Paragonimiasis

Differentiating Feature of Diseases Causing Raised ADA levels

Category / Condition	Mechanism of ADA Elevation	Typical ADA Pattern	Clinical Notes / Differentiation Points
1. Empyema / Bacterial Parapneumonic Effusion	Polymorphonuclear leukocyte activation (ADA mainly from neutrophils)	Very high ADA (>70–100 U/L), predominantly ADA-1 isoenzyme	Usually **neutrophilic** fluid, low glucose, low pH, positive bacterial culture. Rapid resolution with antibiotics distinguishes it from TB.
2. Rheumatoid Pleuritis	Chronic inflammatory lymphocytic effusion due to autoimmune process	Moderately high ADA (40–70 U/L)	Associated with high **rheumatoid factor, low pleural glucose, and very low complement levels.** Consider

			rheumatoid nodules on pleura.
3. Lymphoma / Leukemia (especially T-cell)	Proliferation of lymphoid cells → increased ADA from lymphocyte turnover	Often high (>60 U/L)	Cytology is positive for malignant cells; ADA may mimic TB; look for **LDH >1000 IU/L**, high protein, atypical cells.
4. Malignant Pleural Effusion (adenocarcinoma, mesothelioma)	Tumor infiltration and local inflammation	Usually mild–moderate rise (35–70 U/L)	ADA rise less marked than TB; **cytology positive, LDH and CEA elevated.**
5. Parapneumonic effusion (non-purulent stage)	Activated macrophages and neutrophils	40–60 U/L	May overlap with TB ADA levels; clinical course and bacterial infection signs guide diagnosis.
6. Systemic Lupus Erythematosus (SLE) Pleuritis	Immune complex–mediated lymphocytic inflammation	40–70 U/L	Coexisting ANA positivity, low complement (C3/C4), female predominance, multisystem signs of SLE.
7. Fungal or Viral Infections (e.g., Histoplasmosis, Parvovirus B19, CMV, EBV)	T-lymphocyte stimulation	Variable (moderate)	Rare; mostly immunocompromised hosts; confirm with serology or PCR.
8. Empyema secondary to ruptured abscess or trauma	Local inflammatory response with PMN infiltration	Very high (>100 U/L)	Clinical history of trauma or abscess rupture; purulent fluid.
9. Chylothorax / pseudochylothorax	Chronic pleural inflammation with lymphocytic exudate	35–60 U/L	Milky fluid; high triglycerides; ADA elevation mild, not diagnostic for TB.
10. HIV-associated lymphocytic effusions (non-TB)	Polyclonal immune activation	40–70 U/L	Consider opportunistic infections; correlation with CD4 count.
11. Sarcoidosis	Granulomatous inflammation similar to TB	Moderate ADA elevation (35–70 U/L)	Usually accompanied by non-caseating granulomas, ACE

			elevation, and negative AFB/NAAT.
12. Parasitic infections (e.g., Paragonimiasis)	Eosinophilic pleural reaction	Moderate ADA elevation	Eosinophilia in pleural fluid helps differentiate; endemic areas important clue.
Active TB Disease (Other Rare Tests)			
Cytokine/Chemokine Profiles (e.g., IFN-, TNF-, IL-6)	Measures the concentration of various signaling molecules released by immune cells in response to MTB.	Research tool for studying disease progression, identifying high-risk LTBI, and assessing treatment response.	No single cytokine is a routine diagnostic test due to variability. IGRAs (which measure IFN-release) are the most established form of this principle.
IP-10 (CXCL10)	Host chemokine response	Research/adjunct (triage or treatment monitoring)	**Meta-analyses show moderate diagnostic accuracy; promising as adjunct**; not a stand-alone replacement for NAAT/culture.
(IP-10) ELISA / Lateral Flow	Host immune biomarker (IP-10 chemokine)	Blood, plasma	**Principle:** Measures IP-10 secreted after TB antigen stimulation. **Advantages:** High correlation with IGRA; useful in immunocompromised. **Limitations:** Expensive, research-based, not standardized for routine use.
Cytokine Signature Panels (multi-marker immunoassays)	Host immune responses (TNF-α, IL-2, etc.)	Serum, plasma	**Principle:** Multiplex ELISA to differentiate latent vs active TB. **Advantages:** Emerging diagnostic potential. **Limitations:** Still under research; not standardized clinically.

Flow Cytometry (T-cell Activation Marker assay, e.g., CD27, CD38, HLA-DR)	Activated T-cells specific to MTB antigens	Peripheral blood	**Principle:** Flow cytometric quantification of MTB-specific activated T cells. **Advantages:** May distinguish latent vs active TB. **Limitations:** Expensive, research-only; requires flow cytometry setup.
Extrapulmonary TB diagnostics (biopsy, fluid analysis, etc.)			
For TB outside lungs (e.g., pleura, CSF, lymph nodes)		Tissue biopsy, pleural fluid, CSF, etc. + culture/NAAT	More invasive; variable diagnostic yield depending on site and test used
Various Tests and their Utility in EPTB, what it detects, specimens that may be applied, Principle, Diagnostic Features, Clinical Utility, Limitations			
Platform / Test	**What It Detects**	**Extra Pulmonary Specimens (Examples)**	**Notes (Principle, Diagnostic Features, Clinical Utility, Limitations)**
Fine Needle Aspiration Cytology (FNAC) / Biopsy (Histopathology)	Cytological or histological evidence of granulomatous inflammation ± Acid-Fast Bacilli (AFB)	Lymph node (cervical/axillary), pleura, synovium, bone, liver, bowel, meninges	**Principle:** Microscopic detection of epithelioid granulomas with caseous necrosis and AFB staining (Ziehl–Neelsen). **Findings:** Caseating granulomas suggest TB; non-caseating may need differential (sarcoidosis, fungal). **Advantages:** Diagnostic in up to 80% of TB lymphadenitis; can detect AFB even if culture is negative. Limitations: Invasive; may miss patchy lesions; negative AFB

			doesn't exclude TB. Adjuncts: Send parallel samples for culture, NAAT, and GeneXpert.
Fluid Cytology & Biochemical Analysis	Lymphocytic exudate pattern suggestive of TB	Pleural, pericardial, peritoneal, CSF	**Principle:** Exudative fluid by Light's criteria (high protein, high LDH). - **Findings:** Lymphocytic predominance (>70%), high protein (>3.5 g/dL). **ADA:** >40 U/L suggests TB; but false positives. **Limitations:** Cannot confirm TB without microbiological correlation
Ziehl–Neelsen (ZN) / Auramine–Rhodamine Staining (AFB Smear)	Acid-fast bacilli (M. tuberculosis complex)	Sputum, pleural/peritoneal/pericardial fluid concentrate, tissue	**Advantages:**Simple, inexpensive, specific. **Limitations:** Requires ≥ 5000 bacilli/mL low sensitivity in EPTB (~10–30%).
Culture (MGIT 960 / Löwenstein–Jensen)	Growth of Mycobacterium tuberculosis	Pleural, CSF, peritoneal, lymph node, bone marrow, tissue	**Gold standard** for viable MTB detection and Drug Susceptibility Testing (DST). **MGIT (liquid):** Faster (7–14 days). **LJ (solid):** Slower (3–8 weeks). **Yield:** Pleural (20–40%), CSF (30–50%), Lymph node (50–80%). **Limitations:** Slow; needs biosafety lab.
			Sensitivity: Varies by site (CSF ≈ 60–80%, pleural ≈ 30–50%). **WHO 2023:**

Xpert MTB/RIF & Xpert Ultra (NAAT)	MTB DNA & rifampicin resistance (rpoB gene)	Pleural fluid, CSF, tissue biopsy, lymph node aspirate, urine	Recommended as initial diagnostic test for most EPTB forms. **Limitations:** Negative result does not exclude TB (especially paucibacillary samples).
Line Probe Assay (LPA)	MTB DNA & resistance mutations (rpoB, katG, inhA, gyrA/B, rrs)	Biopsy tissue, pus, aspirate, positive culture	**Limitations:** Requires sufficient bacillary load; costly. Negative results do not exclude TB (especially paucibacillary samples).
Truenat MTB / MTB Plus / MTB-RIF Dx	MTB DNA & rifampicin resistance	Pleural, CSF, tissue	**WHO**-approved as alternative to Xpert in low-resource EPTB settings. Approved only in India.
Adenosine Deaminase (ADA) Estimation (See Above Also)	Enzyme activity from activated T-lymphocytes	Pleural, peritoneal, pericardial fluid	**Cut-off:** >40 U/L (pleural TB); >35 U/L (peritoneal TB). **Sensitivity:** 85–95%, **Specificity:** 85–90%. **False positives:** Empyema, lymphoma, RA, SLE. **Use:** Best in high-prevalence settings; adjunctive test.
Interferon-γ in Body Fluids	IFN-γ release in response to MTB antigens	Pleural, peritoneal, CSF	**Cut-off:** >140 pg/mL suggests TB effusion. **Advantages:** High sensitivity/specificity (~90%). **Limitations:** Costly, limited availability.
			Advantages: Detects even nonviable organisms; useful in smear-negative,

PCR for IS6110 / MPB64 genes	MTB-specific DNA	Pleural fluid, CSF, tissue	culture-negative cases. **Limitations:** Contamination risk; standardization issues; not quantitative.
CSF Biochemical Analysis	Pattern of tuberculous meningitis	CSF	**Findings:** Lymphocytic pleocytosis (100–500/mm^3), protein ↑ (100–500 mg/dL), glucose ↓ (<50% of serum). **ADA:** >10 U/L supports TBM. **Combine:** Xpert Ultra + culture + imaging for confirmation.
			Findings: Ring-enhancing tuberculomas, meningeal enhancement, vertebral collapse, epidural abscess. **Advantages:** High sensitivity; defines extent of disease; guides biopsy. **False Positive in Brain:** Neurocysticercosis (NCC), Fungal granuloma, Metastasis, Pyogenic abscess, Carcinomatous meningitis, Sarcoidosis, Miliary metastases, Toxoplasmosis (HIV), Viral encephalitis, Autoimmune limbic encephalitis.

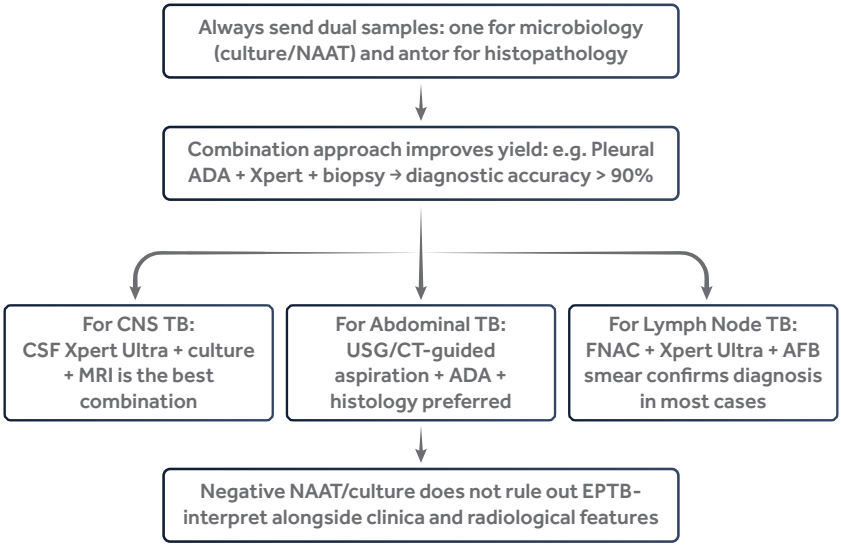
MRI Brain / Spine (for CNS & Pott's disease)	Structural and meningeal lesions	Brain, spinal cord, vertebraea	**Spine:** Pyogenic spondylitis, Epidural abscess, Metastasis, Lymphoma, Brucellar spondylitis **Clues Suggestive of TB:** Sub-ligamentous spread across multiple vertebral levels is highly suggestive of tuberculous spondylitis, reflecting the typical contiguous, anterior vertebral body involvement. Visualization of a thin, smooth-walled paravertebral or psoas "cold abscess" further supports TB, as pyogenic abscesses tend to have thick, irregular walls. Distinct predilection for the anterior vertebral body and adjacent disc space represents the classic paradisal pattern of spinal tuberculosis. Basal meningeal enhancement with or without hydrocephalus is the hallmark of tuberculous meningitis, while the "target sign" on post-contrast MRI—showing a central area of caseation surrounded by a ring of enhancement surrounded by a ring of

			enhancement (characteristic of a tuberculoma). TB lesions typically exhibit slow progression with minimal systemic toxicity, contrasting with the acute, destructive nature of pyogenic infections.
Ultrasound / CT Abdomen	Organ lesions, ascites, lymphadenopathy	Liver, spleen, peritoneum, kidney	**Findings:** Hypoechoic lesions ("microabscesses"), septated ascites, necrotic lymph nodes. **Use:** Guides aspiration for culture and ADA testing.
Histopathology with IHC (Immunohistochemistry)	Granulomatous inflammation; MTB antigen	Biopsy tissue	**Principle:** Immunostaining for mycobacterial antigens (e.g., anti-MPT64). **Advantages:** Increases specificity when ZN negative. **Limitations:** Needs specialized reagents; not routine.

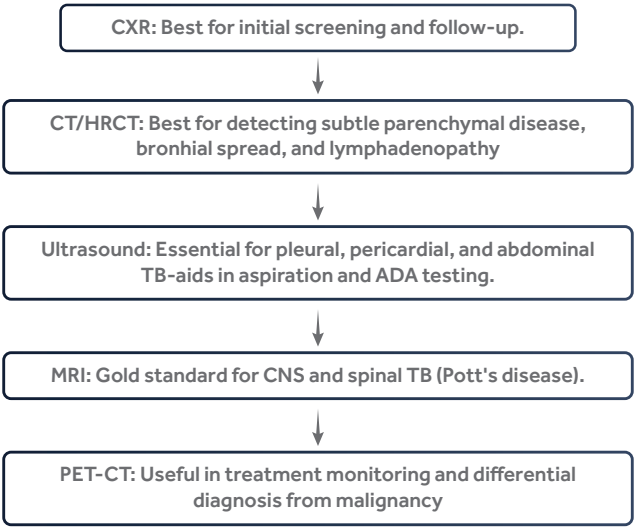
References:

1. Centers for Disease Control and Prevention (CDC). Clinical and laboratory diagnosis for tuberculosis [Internet]. Atlanta (GA): CDC; [cited 2025 Oct 21]. Available from: https://www.cdc.gov/tb/hcp/testing-diagnosis/clinical-and-laboratory-diagnosis.html
2. World Health Organization (WHO). WHO operational handbook on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection [Internet]. Geneva: World Health Organization; 2021 [cited 2025 Oct 21]. Available from: https://www.who.int/publications/i/item/9789240029415
3. The Global Health Network; Treatment Action Group. Tuberculosis diagnostic tools [Internet]. Oxford: The Global Health Network; 2023 [cited 2025 Oct 21]. Available from: https://tghncollections.tghn.org/tb-diagnostic-tools/

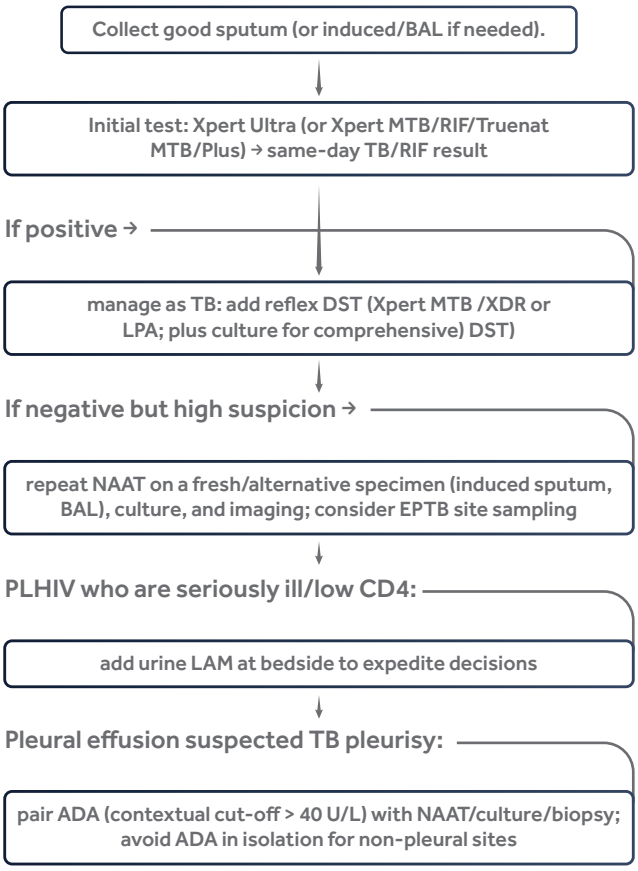
Flow Chart for EPTB Workup



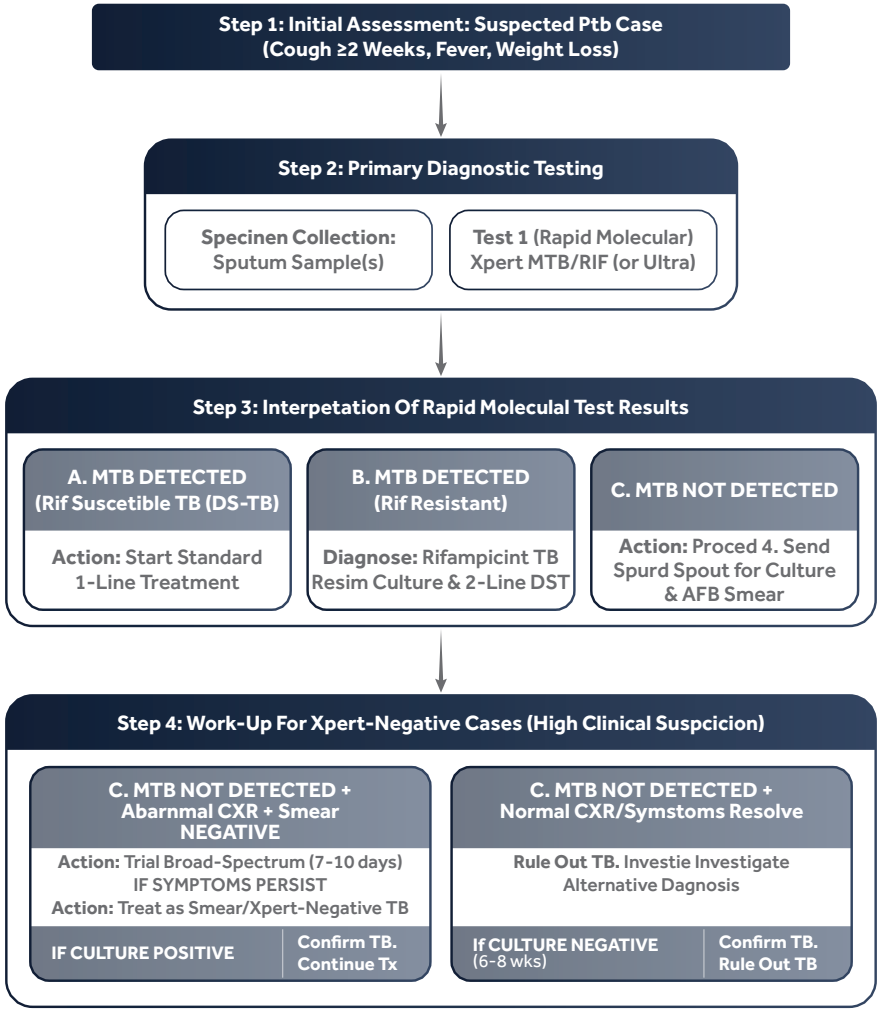
Flow Chart for Selection of Radiology



Diagnostic algorithm (adult pulmonary TB; high-burden setting



Management Algorithm for High Burden Country



Chapter 06:
Management of Tuberculosis

General Principles of Tuberculosis Treatment

Rationale and Goals

1. The primary goals of tuberculosis (TB) treatment are:
2. To cure the individual patient.
3. To prevent death from active TB or its complications.
4. To reduce the risk of relapses after completion of treatment.
5. To interrupt transmission of Mycobacterium tuberculosis to others.
6. To prevent development and spread drug resistance.

Large bacterial populations of M. tuberculosis contain a small fraction of naturally resistant mutants (10^{-6} to 10^{-8}) to any single drug. If a patient is treated with only one or two drugs, the susceptible bacilli are killed, but resistant mutants survive and multiply, leading to drug resistance. In contrast, when four effective drugs are given together, the probability that bacilli are resistant to all is extremely low, ensuring eradication of the bacterial population including resistant subclones.

Therefore, the standard treatment for drug-susceptible TB (DS-TB) consists of:

- An intensive phase of four drugs (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) for two months.
- A continuation phase of two drugs (Isoniazid and Rifampicin) for four months.

With this regimen, approximately 85% of patients achieve a successful treatment outcome.

Anti-TB Drugs (First-Line Anti-TB Drugs)

Drug	Mechanism of Action	Clinical Information	Standard Adult Dose
Isoniazid (H)	Inhibits synthesis of mycolic acids (essential component of mycobacterial cell wall).	Highly bactericidal for rapidly dividing bacilli. Resistance develops quickly if used alone. Major side effects: hepatitis, peripheral neuropathy (prevented by pyridoxine).	5 mg/kg (max 300 mg daily)
Rifampicin (R)	Inhibits DNA-dependent RNA polymerase → blocks RNA synthesis.	Bactericidal for both extracellular and intracellular bacilli. Key sterilizing drug.	10 mg/kg (max 600 mg daily)

		Side effects: hepatotoxicity, drug interactions (CYP450 inducer), orange discoloration of body fluids.	
Pyrazinamide (Z)	Converted to pyrazinoic acid in acidic medium → disrupts membrane potential and energy metabolism.	Bactericidal in acidic environment (effective against dormant bacilli in macrophages). Side effects: hepatotoxicity, hyperuricemia, arthralgia.	25 mg/kg (max 2 g daily)
Ethambutol (E)	Inhibits arabinosyl transferase → impairs cell wall arabinogalactan synthesis.	Bacteriostatic. Used to prevent resistance when bacterial load is high. Side effects: optic neuritis (loss of red-green color vision).	(max 1.6 g daily)

Fixed-Dose Combinations Drugs (FDCs):
It is recommended that Fixed-Dose Combinations Drugs (FDCs) with proven bioavailability, should be used to treat tuberculosis. Evidence suggests that they reduce treatment failure, improve adherence and minimize the risk of drug resistance.

FDCs are patient-friendly due to lower pill burden. They reduce prescription errors, lower the risk of resistance, and simplify programmatic management by streamlining drug forecasting, supply, and dispensing, while minimizing training needs.

Regimen Dosages With Fixed-Dose Combinations In Adults

Patient Body weight (kg)	Initial Intensive Phase Daily (2 months)	Continuation Phase Daily (4 months)
	HRZE (75+150+400+275)	HR (75+150)
30-39	2	2
40-54	3	3
55 & above	4	4

Individual Drug Formulations:
Individual drug formulation is indicated in specific clinical scenarios where FDCs are unsuitable due to their inflexible dosing. Besides, single-drug formulations are critical for addressing drug toxicity, enabling the sequential reintroduction of medications to identify the causative drug.

Recommended Regimens for Drug-Susceptible Tuberculosis (DS-TB) in Pakistan
Initial Intensive Phase: 2HRZE i.e., Isoniazid, Rifampicin, Pyrazinamide and Ethambutol daily for 2 months.

Continuation phase: 4HR i.e., Isoniazid, Rifampicin daily for 4 months.

This regimen is recommended in following cases:

1. Bacteriologically confirmed rifampicin sensitive new PTB patients.
2. Bacteriologically confirmed new TB patient with unknown rifampicin status
3. Bacteriologically confirmed rifampicin sensitive and INH sensitive PTB patients (Irrespective of previous TB treatment).
4. Clinically diagnosed PTB patient (Irrespective of previous TB treatment).
5. Extrapulmonary TB (except CNS, bone or joint TB, where some expert groups suggest longer therapy)

WHO also recommends the 4-month regimen HPMZE comprises 2months of isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 2 months of rifapentine, isoniazid and moxifloxacin. This regimen is recommended for all patients aged above 12 years, regardless of the severity of TB disease. However, it is not recommended under programmatic conditions in Pakistan due to high fluoroquinolone resistance.

Treatment Of Rifampicin Sensitive Isoniazid Resistant Tb (Hr-Tb)

TB patients with a history of previous treatment have a higher risk of drug resistance; therefore, rifampicin testing must be performed in this group. Those found to have rifampicin-sensitive TB should undergo additional testing for isoniazid and fluoroquinolone resistance. The treatment of INH resistant or INH resistance unknown is as follows:

Resistance Pattern	Treatment Regimen	Duration
INH-resistant, RIF-sensitive (FQ-sensitive or unknown)	HRZE + Levofloxacin	6 months
INH-resistant, RIF-sensitive (FQ-resistant)	HRZE	6 months
Bacteriologically confirmed TB, unknown INH status, previously treated (excluding relapse)	RHZE	6 months

Monitoring During Treatment

All **bacteriologically confirmed** or **clinically diagnosed drug-susceptible TB (DSTB)** cases should be monitored by sputum AFB smear.

- **Bacteriologically Confirmed PTB:**
  Sputum smear microscopy should be performed at the end of the 2nd, 5th, and 6th months.
- **Clinically Diagnosed PTB:**
  Sputum smear microscopy should be done at the end of the 2nd month. If negative, no further sputum monitoring is required. They should be monitored clinically like body weight.

Sputum Examination For Treatment Monitoring

Patient Type	Test	Frequency
Pulmonary TB	AFB -microscopy	1)For bacteriologically confirmed PTB, perform AFB smear at the end of months 2, 5, and 6 of follow-up. 2) For clinically diagnosed PTB perform AFB microscopy at the end of month 2 of follow up.
Pulmonary TB	Xpert MTB/RIF assay	**Perform only if:** 1) follow up smear is positive in Bacteriologically confirmed PTB and MTB/RIF -ultra was not done OR Rifampicin result was indeterminate at 0 month. 2) Follow up smear is positive in clinically diagnosed PTB
Pulmonary TB: if the patient does not improve clinically, or at any other times if failure is suspected because of possible drug-resistance	AFB Culture and DST	At the end of the second month and at the end of treatment.

Management Of New Tb Patients With Interrupted Treatment:

Patients do report after interruption of their TB treatment. Following is the chart mentioning how to manage them.

Management Of New TB Patients With < 1 Month Interrupted Treatment

Length of interruption	AFB Smear		Xpert MTB/Rif		Further DST	Treatment
	To do	Result	To do	Result		
Scenario 1: Length of treatment before interruption is less than one month						
<4 weeks	No	NA	No	NA		Continue same treatment & complete 60 doses of intensive phase
4-8 weeks	Yes	Pos/Neg	Yes	RS-TB	No	Restart again on 6-month DS-TB treatment (or Hr-TB if patient was on Hr-TB before interruption)
				MTB not done	No	
				RR-TB	Yes	Refer to PMDR site for RR-TB treatment
>8 weeks	Yes	Pos/Neg	Yes	RS-TB	No	Restart again on 6-month DS-TB treatment (or Hr-TB if patient was on Hr-TB before interruption)
				MTB not done	No	
				RR-TB	Yes	Refer to PMDR site for RR-TB treatment

Management Of New TB Patients With > 1 Month Interrupted Treatment

Length of interruption	AFB Smear		Xpert MTB/Rif		Further DST	Treatment
	To do	Result	To do	Result		
<4 weeks	No	NA	No	NA		Continue same treatment & complete 60 doses of intensive phase
4-8 weeks	Yes	Pos/Neg	Yes	RS-TB	Yes: INH & FQ	Based on INH result, restart on 6-month DS-TB treatment (or Hr-TB if patient was on Hr-TB before interruption)
				MTB not done	No	
				RR-TB	Yes	Refer to PMDR site for RR-TB treatment
>8 weeks	Yes	Pos/Neg	Yes	RS-TB	No	Restart again on 6-month DS-TB treatment (or 6-month treatment of
				MTB not done	No	

						Hr-TB
				RR-TB	Yes	Refer to PMDR site for RR-TB treatment

Follow-up: Subsequent relapse is rare when patients complete the prescribed course of chemotherapy. They should be asked to report for re-examination if symptoms recur.

Chapter 07:

TB Treatment in Special Populations and Situations

Tuberculosis treatment principles remain uniform; however, specific clinical conditions and vulnerable populations require tailored approaches to ensure safety, efficacy, and treatment success.

Pregnancy and Lactation

- **General Principles**
  - Pregnancy is not a contraindication to standard DSTB regimens. Treatment should not be delayed as maternal disease increases risk of maternal mortality, low birth weight, and congenital TB.
  - Breastfeeding is not contraindicated; mothers should be supported to continue while on first-line therapy.
- **Drug Considerations**
  - Isoniazid (H), Rifampicin (R), Ethambutol (E): considered safe in pregnancy.
  - Pyrazinamide (Z): WHO and NTP endorse its use; no teratogenicity reported.
  - Streptomycin and aminoglycosides: contraindicated due to ototoxicity risk to the fetus.
- **Supplementation**
  - Pyridoxine (Vitamin B6) 25–50 mg daily should be co-prescribed with isoniazid to prevent neuropathy.
- **Contraception**
  - Rifampicin induces hepatic enzymes and may reduce hormonal contraceptive efficacy. Barrier methods or non-hormonal contraception should be advised.

Tuberculosis with Liver Disease

- Rationale: Hepatotoxicity risk is increased due to overlap of TB drugs and underlying hepatic dysfunction.
- In chronic liver disease, Child-Pugh score is used to assess severity of liver disease.

Child–Pugh Score (for Cirrhosis Severity)

Parameter	1 point	2 points	3 points
Total bilirubin	< 2 mg/dL (< 34 µmol/L)	2–3 mg/dL (34–50 µmol/L)	> 3 mg/dL (> 50 µmol/L)
Serum albumin	> 3.5 g/dL	2.8–3.5 g/dL	< 2.8 g/dL
Prothrombin time (sec prolonged) OR INR	< 4 sec OR < 1.7	4–6 sec OR 1.7–2.3	> 6 sec OR > 2.3
Ascites	None	Mild (controlled)	Moderate–Severe (refractory)
Encephalopathy	None	Grade I–II (mild–moderate)	Grade III–IV (severe)

Interpretation

- **Class A (5–6 points):** Well-compensated disease (1-year survival ~100%)
- **Class B (7–9 points):** Significant functional compromise (1-year survival ~80%)
- **Class C (10–15 points):** Decompensated disease, poor prognosis (1-year survival ~45%)

- **Mild Liver Disease (Child–Pugh A)**
  - Standard 6-month regimen may be used with careful monitoring.
  - Baseline liver function tests (LFTs) and monthly monitoring are mandatory.
- **Moderate Liver Disease (Child–Pugh B)**
  - Avoid regimens containing all three hepatotoxic drugs (H, R, Z).
  - Suggested regimen: 9–12 months of H + R + E (without Z), or inclusion of fluoroquinolone if needed.
- **Severe Liver Disease (Child–Pugh C)**
  - Avoid hepatotoxic drugs if possible.
  - Consider regimens using E + Streptomycin + fluoroquinolone ± other non-hepatotoxic agents for 18–24 months.
  - Such patients should ideally be managed in collaboration with hepatology specialists.

Severity (Child–Pugh)	Recommended Approach	Drug Considerations	Monitoring
Mild (A)	Standard 6-month regimen (HRZE → HR)	All drugs may be used	Baseline + monthly LFTs
Moderate (B)	Avoid triple hepatotoxicity	H + R + E (9–12 mo) ± fluoroquinolone	Baseline + 2-weekly LFTs for first 2 month
Severe (C)	Avoid hepatotoxic drugs if possible	E + Streptomycin + Fluoroquinolone ± others for 18–24 months	Monthly LFTs; specialist input mandatory

Tuberculosis with Renal Failure

- **Principles:** Most first-line TB drugs are hepatically metabolized, except E and Z which are renally excreted.

- **Drug Adjustments**
  - Isoniazid, Rifampicin: no dose adjustment required.
  - Ethambutol: reduce dose if eGFR <30 mL/min (e.g., 15 mg/kg 3×/week).
  - Pyrazinamide: reduce to 20 mg/kg 3×/week if severe renal impairment.
  - Aminoglycosides (Streptomycin, Kanamycin): avoid due to nephrotoxicity.
- **Dialysis Considerations**
  - Administer drugs after hemodialysis sessions on dialysis days.
  - Avoid dosing just before dialysis to prevent drug loss.

- **Monitoring**
  - Monthly renal profile and vision testing (for ethambutol).

Drug	Mild CKD (eGFR >30)	Severe CKD (eGFR <30 / Dialysis)	Notes
Isoniazid	No change	No change	Give after dialysis
Rifampicin	No change	No change	Hepatic metabolism
Ethambutol	15 mg/kg daily	15 mg/kg 3×/week	Monitor vision
Pyrazinamide	No change	20 mg/kg 3×/week	Give after dialysis
Streptomycin/Aminoglycosides	Avoid if possible	Contraindicated	High ototoxic/nephrotoxic risk

Tuberculosis with HIV Co-Infection

- **General Principles**
  - Co-infection worsens morbidity and mortality; hence, early ART initiation is essential.
  - Management requires coordination between TB and HIV programs.
- **Timing of ART Initiation in TB patients:**

	Art Initiation Timing
Tuberculosis	Within the first 2 weeks if CD4 count < 50/mm^3
	Within the first 8 weeks if CD4 count > 50/mm^3

- **Opportunistic**
- **Infections ART Initiation**
- **Drug–Drug Interactions**
  - Preferred ART with rifampicin: Tenofovir (TDF) + Lamivudine (3TC) (or Emtricitabine (FTC) + Efavirenz (EFV).
  - Rifampicin reduces levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).
  - Nevirapine should be avoided with rifampicin.
  - Dolutegravir can be used with rifampicin but requires dose adjustment (50 mg twice daily).
- **Adjuvant care**
  - Cotrimoxazole prophylaxis (CPT) is recommended in all HIV/TB patients.
  - Pyridoxine supplementation (25–50 mg/day).

Chapter 08:
Treatment Adherence and Outcomes in TB Through DOT and Patient-Centered Support

Directly Observed Therapy (DOT)

- Remains the cornerstone of adherence strategy in Pakistan.
- It can be clinic-based, community-based, or home-based depending on patient circumstances.
- Digital adherence technologies (e.g., SMS reminders, video-DOT) may be used as supportive tools.

Patient-Centered Adherence Support

- Health education, counseling, and family engagement.
- Social support mechanisms: transport facilitation, nutritional packages, stipends.
- Flexible clinic timings to accommodate working patients.

Monitoring

- **Clinical:** monthly symptom review, weight charting.
- **Laboratory:** sputum smear/culture at baseline, 2 months, end of treatment.
- **Safety:** baseline LFTs, RFTs in at-risk groups.
- **Active Drug Safety Monitoring and Management (aDSM) principles:** monitor for adverse drug reactions (though primarily for DR-TB, vigilance applies to DSTB as well).

Follow-Up

- After completion, patients should be followed at 6 and 12 months for relapse assessment.
- Use of electronic surveillance systems (NTP's ERS/KP TB-MIS) should be encouraged.

Health Education, Counseling, and Treatment Outcomes

Health Education and Counseling

- **Educate patients and family on:**
  - Nature of disease, transmission, and prevention.
  - Importance of strict adherence to avoid resistance.
  - Recognition of side effects (jaundice, visual blurring, rash).
  - Nutritional and psychosocial support.

Counseling for Stigma Reduction

- TB carries significant social stigma in Pakistan. Counsel families to support patients, avoid isolation, and encourage treatment completion.

Treatment Outcomes

Term	Definition
Cured	A patient registered as smear-positive, has completed the duration of treatment, and becomes sputum smear negative at the end of treatment and on at least one previous occasion.
Treatment completed	A person with TB disease who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure.
Treatment successful	A person with TB disease who was either cured or who completed treatment as defined above.
Treatment Failed	A sputum smears positive patient who remains or becomes sputum smear positive at month five or later.
Died	A person with TB disease who died for any reason before starting (for case outcomes), or during the course of, treatment (for both case and treatment outcomes).
Lost to follow-up	A person with TB disease who did not start treatment (for case outcomes) or whose treatment was interrupted for two consecutive months or more (for both case and treatment outcomes).
Not Evaluated	A person with TB disease to whom no treatment outcome was assigned, excluding those lost to follow up.

References:

1. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022.
2. National Tuberculosis Control Program, Pakistan. National guidelines for tuberculosis control in Pakistan. Islamabad: Ministry of National Health Services, Regulations and Coordination; 2024.

Chapter 09:
Side Effects of ATT & Their Management

Recent cohort studies and meta-analyses reveal:

- 47.9% of patients experience at least one adverse reaction during intensive phase
- Gastrointestinal system is the most affected, followed by nervous system and skin
- Risk factors: age >45, female gender, HIV infection, alcohol use, extrapulmonary TB

General Principles

- **Patient Education:** Advise all patients on potential side effects (especially serious ones, like signs of hepatitis, optic neuritis, or severe rash) and the importance of reporting them immediately.
- **Risk Factors:** Consider closer monitoring for patients with risk factors, including older age (years), alcohol use disorder, pre-existing liver disease (e.g., Hepatitis B/C), malnutrition, HIV co-infection, diabetes, and pre-existing renal impairment.
- **Monitoring:**
  - **Baseline:** clinical review; weight, pregnancy status
  - **AST/ALT, bilirubin** assessment
    - No monthly LFTs for low-risk, asymptomatic adults
    - Do symptom-triggered testing
    - If risk factors frequent monitoring (e.g., fortnightly)
    - High-risk: check LFTs periodically (e.g., monthly or per local policy).
  - Monitor serum creatinine if renal disease is present
  - Monitor visual acuity & color vision (Ishihara chart) before ethambutol in adults
  - Uric acid monitoring is optional for Pyrazinamide.
- **Severity Assessment:** Differentiate between minor (mild, manageable without regimen interruption) and major (severe, potentially life-threatening, requiring drug withdrawal/modification, or hospitalization) ADRs.

Drug-Specific Side Effects and Management Summary

Drug	System	Minor Side Effect	Management (Minor)	Major Side Effect	Management (Major)
Isoniazid (H)	Gastrointestinal	Nausea, vomiting, abdominal pain, loss of appetite.	Take medication with food (if tolerance is an issue, although bioavailability is higher on an empty stomach). Administer anti-emetics if needed.	**Hepatotoxicity:** (See below Combined Management)	STOP all hepatotoxic drugs (H, R, Z). Investigate other causes. Reintroduce drugs sequentially after symptoms/LFTs resolve.

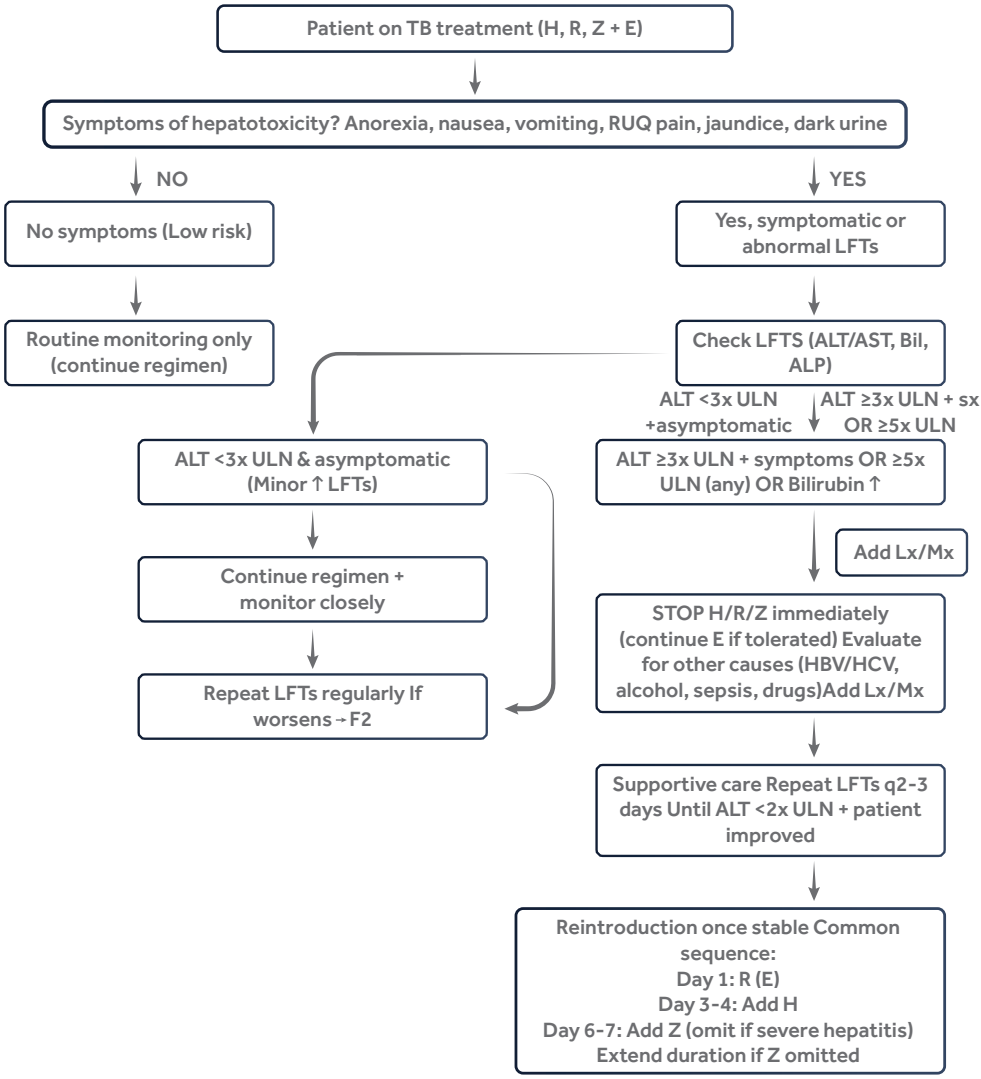
	Nervous System	Mild tingling/numbness of hands/feet (early peripheral neuropathy).	**Prevention/Treatment:** Give **Pyridoxine (Vitamin B6)** 10–25 mg daily to all patients on INH (or 50–100 mg daily for those at high risk: HIV, diabetes, malnutrition, alcoholism, chronic renal failure, or if	Severe peripheral neuropathy (pain, significant motor involvement).	**STOP INH. Increase Pyridoxine** to 100-200 mg daily. Only reintroduce INH with high-dose Pyridoxine (100 mg/day) if essential for the regimen.
			symptoms occur).	Drug-induced Lupus, Psychosis, Optic Neuritis.	**STOP** INH permanently. Consult specialist.
Rifampicin (R)	Gastrointestinal	Mild nausea, vomiting, abdominal cramps.	Take medication with food.	**Hepatotoxicity:** (See below Combined Management)	**STOP** all hepatotoxic drugs (H, R, Z).
	Dermatologic	Cutaneous "flushing" with or without rash/pruritus (usually within hours of dose).	Usually resolves spontaneously. Antihistamines may be used.	**Hypersensitivity Reactions:** Fever, rash (urticaria, purpuric rash, fixed drug eruption), **Severe Cutaneous Adverse Reactions (SCARs)** (e.g., SJS/TEN).	**STOP** RIF immediately. Consult specialist. Do not reintroduce if SCAR is suspected.
	Hematologic	Transient thrombocytopenia, mild flu-like syndrome (fever, chills, headache—especially with intermittent dosing).	Symptomatic treatment (analgesics/antipyretics). Consider changing intermittent regimen to daily.	Thrombocytopenia with bleeding/purpura, Hemolytic Anemia, Acute Renal Failure (usually with intermittent dosing after lapse in therapy).	**STOP** RIF permanently. Consult hematologist/nephrologist.
		Orange/red discoloration	**Patient warning:** This is harmless	**Drug Interactions:** Significant	Adjust doses of concomitant

	Other	of urine, sweat, tears, saliva.	Advice against wearing soft contact lenses (may stain permanently).	interaction with many drugs (e.g., oral contraceptives, HIV protease inhibitors, anticoagulants).	medications or switch to Rifabutin (less induction) or alternative TB regimen.
Pyrazinamide (Z)	Gastrointestinal	Nausea, vomiting, loss of appetite.	Take medication with food.	**Hepatotoxicity:** (See Combined Management) (More common and often higher incidence than H or R).	**STOP** all hepatotoxic drugs (H, R, Z).
	Musculoskeletal	Arthralgia (joint pain) is due to increased serum uric acid (not gout).	Treat with analgesics (NSAIDs, avoiding high-dose aspirin). Continue PZA.	Acute Gouty Arthritis (rare).	Treat with standard gout medications (e.g., allopurinol if severe, or NSAIDs/colchicine). May require PZA withdrawal or dose reduction if severe or recurrent.
Ethambutol (E)	Ocular	N/A		**Optic Neuritis:** (dose-related, usually after 2 months) Decreased visual acuity, red-green color vision impairment, central scotoma.	**STOP** EMB immediately. Refer to ophthalmologist for assessment. Vision loss is usually reversible if caught early; if advanced, it may be permanent. Do not reintroduce.
	Other			Allergic reactions, rash, peripheral neuropathy (rare).	

Detailed Management Protocol for Major Side Effects

1. Drug-Induced Hepatotoxicity (DIH)

Action	Details
Diagnosis/Trigger	STOP all hepatotoxic drugs (H, R, Z, or RPT) immediately if the patient reports symptoms (unexplained anorexia, nausea, vomiting, persistent fatigue, dark urine, jaundice, or abdominal pain) OR if asymptomatic but transaminases (AST/ALT) are: Upper Limit of Normal (ULN) OR ULN with symptoms.
Initial Management	Perform LFTs (AST, ALT, Bilirubin), viral hepatitis serology (if unknown), and test for other causes (e.g., alcohol, acetaminophen, other drugs).
Regimen during Pause	Continue Ethambutol (E) (and/or Fluoroquinolone if used for a substitute regimen) as these are non-hepatotoxic.
Re-introduction Strategy (After resolution of symptoms AND LFTs ULN or near baseline):	Step 1: Reintroduce Rifampicin (R) at a full dose. Monitor LFTs 3–7 days later. If tolerated: Step 2: Reintroduce Isoniazid (H) at a full dose (with Pyridoxine). Monitor LFTs 3–7 days later. If tolerated: Step 3: Reintroduce Pyrazinamide (Z) LAST or consider an alternative regimen if the patient had prior Z-associated severe hepatitis.
Alternative Regimens	If any drug cannot be reintroduced (or patient is high-risk): use a non-hepatotoxic regimen, e.g., (E/Fluoroquinolone and an injectable or other second-line agent for 12–18 months, based on expert consultation.



2. Severe Cutaneous Adverse Reactions (SCARs)

Action	Details
Diagnosis/Trigger	Fever, mucosal involvement, blistering, detachment of epidermis, or progressive rash (e.g., Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
Management	STOP all Anti-TB drugs IMMEDIATELY. Hospitalize patient. Consult dermatologist disease specialist.
Re-introduction	DO NOT REINTRODUCE the causative drug (most commonly RIF, less commonly H). Desensitization is generally contraindicated for SCARs.
Regimen Change	Design a new regimen using drugs with low cross-reactivity, often excluding the initial first-line drugs.

A. Optic Neuritis (Ethambutol)

Action	Details
Diagnosis/Trigger	Blurred vision, central visual field defect, inability to distinguish red-green color, reported by the patient or detected during monthly screening. Dose-related risk increases above 15 mg/kg/day and with renal impairment/older age; adjust dose for eGFR.
Management	STOP Ethambutol (E) IMMEDIATELY. Refer to an ophthalmologist for detailed evaluation.
Re-introduction	Visual acuity and color vision should be monitored closely. Recovery is slow, usually over weeks to months, but may be incomplete if damage is severe.
Regimen Change	E must be permanently discontinued. Continue the regimen with H, R, Z (if tolerated) or substitute E with fluoroquinolone if needed, based on susceptibility and expert opinion).

B. Peripheral Neuropathy (ISONIAZID)

- Prevent in at-risk adults and all pregnant/lactating patients: pyridoxine 25–50 mg/day.
- Treat symptomatic neuropathy: pyridoxine 50–100 mg/day (can increase up to 100–200 mg/day if refractory), continue H if mild and LFTs acceptable; consider dose adjust if severe.

C. Rifampin Hypersensitivity Syndromes

- Flu-like syndrome (fever, myalgias, hypotension) or **immune thrombocytopenia → stop R permanently;** switch to alternative rifamycin (e.g., rifabutin) only with expert input.

Pregnancy: H/R/Z/E generally considered safe when benefits outweigh risks; pyridoxine is essential with INH. Monitor LFTs more closely.
HIV/ART: Expect significant rifamycin–ART interactions. Use updated ARV interaction tables; consider rifabutin or ART adjustment.
Renal impairment: Adjust Ethambutol dose, consider urate-lowering strategies if symptomatic on pyrazinamide.

References:

1.Ramappa V, Aithal GP. Hepatotoxicity related to antituberculosis drugs: mechanisms and management. J Clin Exp Hepatol. 2013;3(1):37–49. doi:10.1016/j.jceh.2012.12.001
2.Dhiman RK, Saraswat VA, Rajekar H, Misra SP, Duseja A, Chawla YK, et al. A guide to the management of tuberculosis in patients with chronic liver disease. J Clin Exp Hepatol. 2012;2(3):260–70. doi:10.1016/j.jceh.2012.07.007
3.Wang YC, Salvador NG, Lin CC, Wu CC, Lin TL, Lee WF, et al. Comparative analysis of drug–drug interaction between immunosuppressants, safety and efficacy of rifabutin from rifampicin-based anti-TB treatment in living donor liver transplant recipients with active tuberculosis. Biomed J. 2021;44(6 Suppl 1):S162–70.
4.Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin, rifabutin, and rifapentine drug interactions. Curr Med Res Opin. 2013;29(1):1–2.
5.Ho CC, Chen YC, Hu FC, Yu CJ, Yang PC, Luh KT. Safety of fluoroquinolone use in patients with hepatotoxicity induced by anti-tuberculosis regimens. Clin Infect Dis. 2009;48(11):1526–33.
6.World Health Organization. Treatment of tuberculosis: guidelines. 4th ed. Geneva: WHO; 2010.
7.Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174(8):935–52.
8.World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: WHO; 2014.

Chapter 10:
TB in Children

A child is a person under 10 years of age, and an adolescent is a person 10-19 years of age. It is estimated that 7.5 million children and young adolescents aged under 15 years are newly infected with M. tuberculosis each year.

After close exposure and in the absence of TPT, the risk of developing TB disease in children (aged under 19 years) is 18%, which usually develop within 2 years of being evaluated as a contact. Younger children, especially those aged under 2 years, are at particularly high risk of TB disease progression after infection. Contact investigation reaches many children too late to prevent disease considering that 80% of pediatric deaths from TB occur in children aged under 5 years,

Earlier diagnosis of infectious adults and timely TB screening, diagnosis and treatment of children who are contacts are important approaches to reduce TB disease and deaths in children.

TB Screening and Contact Investigation

Contact investigation is the systematic identification of people, including children and adolescents, with previously undiagnosed TB disease and TB infection among the contacts of a TB patient. The risk of infection is greatest if exposure to a person with TB disease is close and prolonged (e.g. exposure of an infant or toddler to the mother or other caregiver in the household). Contact investigation and management consist of identification of close contacts, clinical evaluation, testing (where possible), and provision of appropriate TB treatment (for people with TB disease) or TPT (for people without TB disease but with proven or suspected TB infection).

TB Screening in Children

Any child aged under 1O years who has had close contact with a person with TB disease should be screened for TB with a symptom screen or CXR as part of contact investigation. Screening approaches for children who are close contact of a person with TB and children living with HIV.

Symptom Screening

Recommended symptoms for screening are given in the Table below. In addition, in young children, reduced playfulness or lethargy should also be included, since prolonged cough may be absent in children with disseminated disease. It is useful to examine growth charts regularly to determine whether a child has been losing weight or their weight has plateaued. Weight loss or a plateau in weight gain (failure to thrive) should be a warning sign for possible TB.

If any one or more of the symptoms is present, the child is regarded as having a positive screen and should be managed as having presumptive TB. Based on symptom screen alone, about 30% of children may undergo unnecessary diagnostic tests or even treatment for TB.

Recommended Screening Tools

Symptom Screen	Cough >2 weeks, fever >2 weeks, poor weight gain (or weight loss) in past 3 months	Current cough, fever, poor weight gain in past 3 months or close contact with a person who has TB
Timings of Screening	During contact investigation and follow up activities	Every encounter with HCW

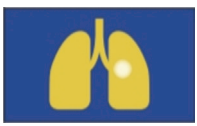
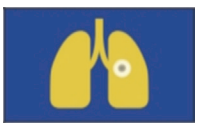
Chest X-ray in Children

CXR is more specific than symptom screening alone in close contacts aged under 15 years. Abnormalities caused by TB seen on CXR in children may differ widely from those in adults. Older children may have adult-type disease presentation, such as lung cavities, but changes on CXR associated with TB disease in younger children may be subtle and hard to see if the quality is not optimal.

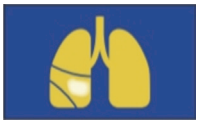
Common CXR abnormalities in children include enlarged hilar and paratracheal lymph nodes, sometimes with evidence of lymph nodes compressing the airways, alveolar consolidation without visible cavities, miliary lesions (as a sign of disseminated disease) and pleural effusions. It may be difficult to distinguish abnormally enlarged paratracheal and hilar lymph nodes from normal vascular structures.

When using CXR for TB screening in children, ideally both PA and lateral views should be done.

Table 6.1: Classification of radiological disease 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	Complicated pleural effusion
	

Alveolar opacification: < 1 lobe



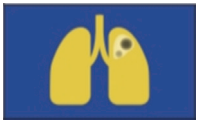
Other:

- Interstitial pneumonia

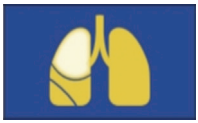
- Perihilar infiltrates

Alveolar opacification: involving a whole lobe or multiple lobes

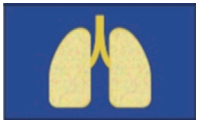
Other:



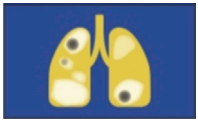
- All cavitary disease



- Expansile pneumonia



- Miliary TB



-TB bronchopneumonia

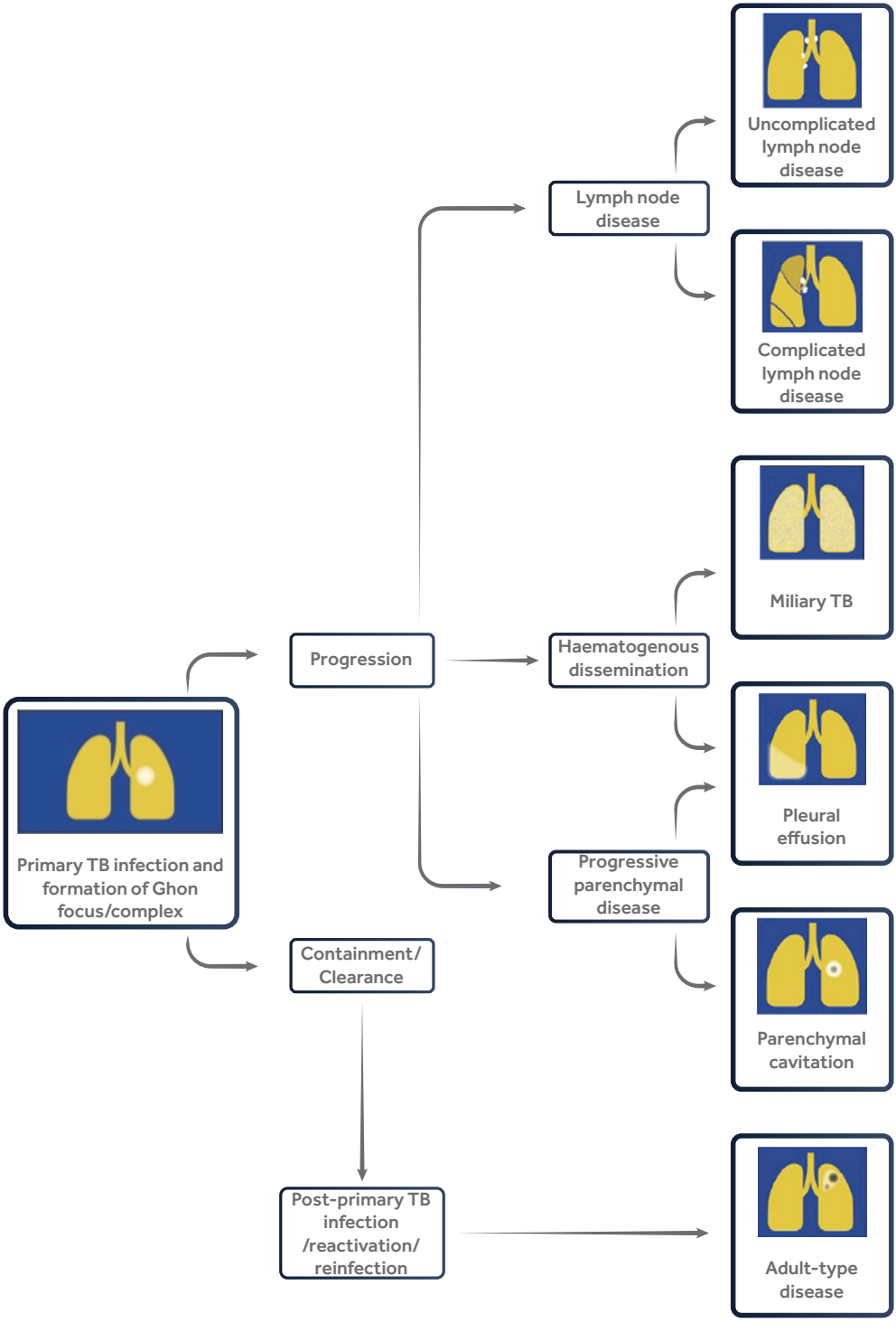


Figure 1: Schematic representation of the pathogenesis of paediatric TB

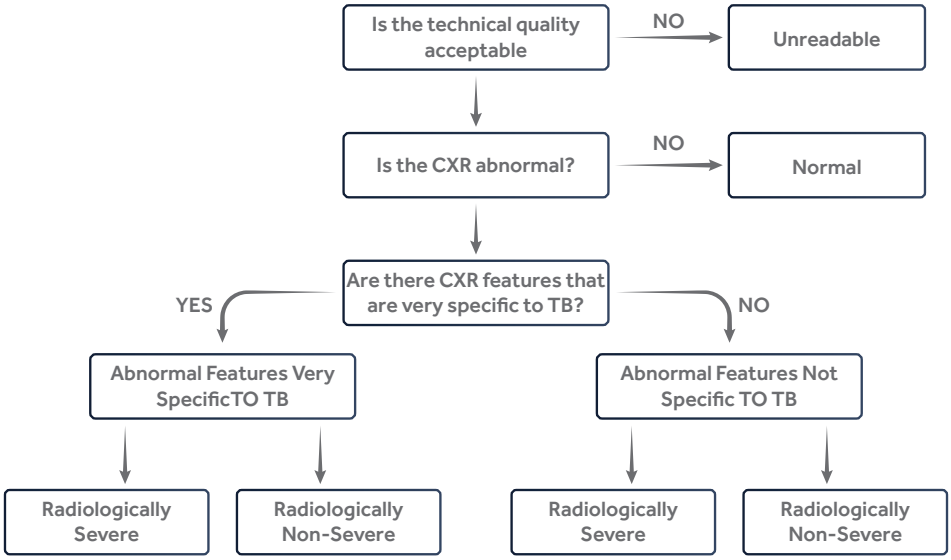


Figure 4.1: Algorithm for CXR interpretation in a child with presumptive pulmonary TB

Children with pulmonary TB often have non-specific CXR features. Always interpret the CXR findings within the full clinical context and remember the value of repeat imaging.

Figure 6.1, 1 & 4.1: Adapted with permission from World Health Organization, Diagnostic CXR Atlas for Tuberculosis in Children: A Guide to Chest X-ray Interpretation. 2nd ed. Geneva: World Health Organization; 2022.

Score sign and symptoms and CXR features			
Sign and symptoms		**CXR**	
Cough longer than 2 weeks	+2	Cavity / cavities	+6
Fever longer than 2 weeks	+5	Enlarged lymph nodes	+17
Lethargy	+3	Opacities	+5
Weight loss	+3	Miliary pattern	+16
Hemoptysis	+4	Effusion	+8
Night sweats	+2		
Swollen lymph nodes	+4		
Tachycardia	+2		
Tachypnea	+1		
SUM A--------		SUM A--------	
Yes	← IF SUM A + SUM B is more than 10 →		No
↓			↓
Initiate appropriate TB tretment		Do not treat for TB follow up after 2weeks	

Tests for TB Infection

TST and IGRA are not recommended to screen for TB disease in children as these tests cannot distinguish TB infection from TB disease and cannot predict who will progress to TB disease. Both tests provide a marker for TB infection but may be influenced by mechanisms unrelated to TB infection and give false-negative or false-positive results.

Prevention Of TB In Children And Adolescents

Preventing TB is crucial, and it can be achieved in children through BCG vaccination, TPT, and TB infection prevention and control.

BCG Vaccination

BCG is a live attenuated bacterial vaccine derived from Mycobacterium Bovis, originally isolated in 1902 from a tuberculous cow. BCG vaccination is recommended in countries like Pakistan with a high incidence of TB. A single dose should be given to all healthy neonates at birth.

The benefits of BCG vaccination include:

- Demonstrated significant effectiveness, but protection has not been consistent against all forms of TB in all age groups.
- Good (up to 90%) protection against severe forms of TB, including TBM and miliary TB, if given during the neonatal period.
- Protection against PTB in children, however it mainly prevents progression to disseminated forms of TB (when given to neonates).

TB Preventive Treatment

Children and adolescents exposed to a person with TB but found not to have TB disease should be assessed for TB infection and eligibility for TPT. It is important to exclude TB disease before initiating TPT.

- Asymptomatic close contacts aged 5 years and over should undergo CXR if available and must complete a detailed evaluation for TB if CXR is abnormal.
- Asymptomatic close contacts aged under 5 years, CXR, is not a requirement before starting TPT.

TB Preventive Treatment Regimen

	< 2 years	>2 years
1	6INH	6INH
2		3HP
3	3HR	3HR

Diagnosis of TB in Children

Children must be evaluated for TB disease who:

- Screen positive during contact investigation or at health facility-based screening.
- Present to a health care facility with signs and symptoms of TB.
- Are identified as having presumptive TB.

It is important to take a careful history of the known exposures of the parent or caregiver and child. Household contacts are often considered, but, with a high TB incidence like in Pakistan, close contact can occur in a variety of community settings, including school, daycare and religious settings. A high index of suspicion of TB in young children should be maintained.

Pakistan Pediatric Association (PPA) Recommended Scoring Chart for Diagnosis of TB in Children:

Diagnosing TB in children and adolescents	
History	TB contact (especially in the past 12 months), previous TB Treatment
Signs and symptoms	The most common symptoms of TB in children are Cough, especially if persistent and not resolving Prolonged fever with or without night sweats not eating well or anorexia Weight loss or failure to thrive Unusual fatigue, reduced playfulness or decreased activity
Chest Xray	CXR is useful to support the clinical diagnosis of PTB when TB is presumed, and bacteriological testing is negative e.g. in very young children.
Clinical examination	Vital signs, Growth assessment and assessment of pulmonary disease by auscultation and percussion, assessment of signs of respiratory distress and assessment for relevant extrapulmonary TB.
Bacteriological examination	In children with signs and symptoms of pulmonary TB, Xpert Ultra should be used as the initial diagnostic test for TB and detection of rifampicin resistance on sputum, nasopharyngeal aspirate, gastric aspirate or stool, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST)

PPA recommends scoring chart for diagnosis of CHTB. Specimen collection is challenging in children:

Score	1	2	3	4	5
Age 1	< 5 years I				
Close Contact*	TB suggestive	Clinically diagnosed TB case (B-ve)	Bacteriologically positive PTB		

PEM/SAM**	Yes	Not responding to Nutritional rehabilitation for 02 months			
H/O Measles /Whooping cough	3-6 months	< 3 months			
HIV positive		Yes			
Immuno-compromised***	Yes				
Clinical Manifestation*****		Suggestive		Strongly suggestive	
Radio Diagnostic imaging*******	Non- specific	Suggestive of TB	Strongly suggestive		
Tuberculin Skin /PPD	5-10 mm		> 10mm		
Xpert test					Positive for TB
Histopathology- Granuloma	Nonspecific				Positive for TB

Interpretation Of PPA Scoring Chart:

0-2	Unlikely TB	• Investigate other reasons of illness
3-4	Possible TB	• Do not treat for TB • Manage the presenting symptom(s) • Monitor monthly the condition(s) for 3 months using scoring chart
5-6	Possible TB	• Investigate and exclude other causes of illness • Investigation may justify therapy • Start ATT if positive on GeneXpert or Granuloma seen
17 or more	Possible TB	• Confirm (if possible)

Note: Based on symptom screen alone, about 30% of children may undergo unnecessary diagnostic tests or even treatment for TB. The risk of a false-positive diagnosis of TB is higher among children than adults because diagnosis of CHTB is frequently made solely on clinical grounds. HCWs should nonetheless remain vigilant to possible false-positive TB diagnoses among children, monitor responses to treatment carefully, and consider alternative diagnoses, especially if a child is not improving on treatment. If a plausible

alternative diagnosis is confirmed, providers may consider stopping TB treatment while remaining mindful that TB may coexist with other diseases.
TB treatment should never be used as a "trial of treatment."

Treatment of TB in Children
As in adults, TB treatment in children and adolescents includes a 2-month intensive phase followed by a continuation phase of 4 months.
Infants aged 0-3 months with presumptive or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants.

Pulmonary TB Treatment Regimens by Age Group, Disease Severity and Local Epidemiology:

		Intensive Phase		Continuation Phase
Infants aged <3 months or weighing <3 kg				
PTB of any severity		2HRZ or 2HRZE		
Children and adolescents aged 3 months to <12 years				
PTB with non-severe TB disease	I	2HRZ(E)		2HR
Severe PTB		2HRZEc		4HR
Adolescents aged 12-<16 years				
Severe PTB		2HRZE		
Adolescents aged 16-<20 years				
PTB of any severity		2HRZE		

Treatment regimens for extra-pulmonary TB:

	Treatment Regimen	
	Intensive Phase	Continuation Phase
Infants aged <3 months or weighing >3 kg		
Peripheral lymph node TB	2HRZ or 2HRZE	4HR
Children and adolescents aged 3 months-<16 years		
Peripheral lymph node TB*	2HRZ or 2HRZE	2HR
Adolescents aged >16 years		
Peripheral lymph node TB	2HRZ or 2HRZE	4HR
Children and adolescents aged 0-19 years		
EPTB b	**2HRZE**	**4HR**
TB Meningitisc	**2HRZE**	**10HR**
Osteoarticular TB	**2HRZE**	**10HR**

Weight Band Table Using Widely Available Dispersible FDC:

			less Than **2kg**	2-2.9	3-3.9	4-7.9	8-11.9	12-15.9	16-24.9
		Duration in Months							
Intensive Phase	HRZ (50/ 75/ 150)	2	1/4	1/2	¾	1	2	3	4
	E 100	2	1/4	1/2	3/4	1	2	3	4
Continuation Phase daily	HR (50/ 75)	4	1/4	1/2	3/4	1	2	3	4

References:

1.World Health Organization. WHO consolidated guidelines on tuberculosis: Module 5 — Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022.
2.Pakistan Pediatric Association (PPA). National guidelines for management of tuberculosis in children. Karachi: Pakistan Pediatric Association; 2023.
3.World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: World Health Organization; 2014.
4.World Health Organization. Diagnostic CXR Atlas for Tuberculosis in Children: A guide to chest X-ray interpretation. 2nd ed. Geneva: World Health Organization; 2022
5.World Health Organization. BCG vaccines: WHO position paper – February 2018. Wkly Epidemiol Rec. 2018;93(8):73–96.
6.Pakistan National TB Control Program (NTP). National guidelines for the management of tuberculosis. Islamabad: Ministry of National Health Services, Regulations & Coordination; 2023.

Chapter 11:
TB Contact Management

The purpose of TB contact management is to identify, evaluate, and manage individuals who have been exposed to an infectious tuberculosis (TB) case. Early detection of secondary TB cases and provision of tuberculosis preventive treatment (TPT) to eligible contacts are key strategies to break the chain of transmission and reduce disease burden in the community.

Person-to-person transmission of Mycobacterium tuberculosis occurs via inhalation of droplet nuclei (airborne particles 1–5 µm in diameter). Activities such as coughing, sneezing, and singing facilitate formation of droplet nuclei and increase the risk of transmission.

Factors associated with an elevated risk of TB transmission include:

- Presence of active, untreated pulmonary or laryngeal TB
- Cavitary disease on chest imaging
- Positive sputum for M. tuberculosis on GeneXpert MTB/Rif, AFB smear, or culture
- Patients within the first two weeks of starting ATT
- High risk of TB reinfection within the first two years after treatment
- Immunocompromised patients (e.g., HIV-positive) with extrapulmonary TB

Preventive Measures for the Spread of TB Infection

1.Cough hygiene: TB patients should cover their mouth and nose with a mask, tissue, or forearm while coughing or sneezing.
2.Isolation: Hospitalized TB patients should be kept in isolation rooms with adequate air circulation (at least 12 air exchanges per hour). If natural ventilation is not feasible, HEPA filters should be used.
3.Respiratory protection: Health care workers should use N95 respirators while visiting or performing invasive procedures (e.g., bronchoscopy) on infectious TB patients.
4.Environmental controls: Germicidal ultraviolet (GUV) systems may be installed in healthcare facilities to reduce airborne transmission where feasible.

Principles of Contact Investigation/Management

Index Case
The index case is the initially identified person with smear positive TB who serves as the starting point for the investigation.
In contact investigation, priority should be given to Children <5 years, HIV-positive contacts, and immuno-compromised individuals.

Close Contact
A person who does not live in the same household as a person with TB but who has shared an enclosed space, such as a social gathering place, workplace or facility, with the index patient for extended periods during the day during the 3 months before the current disease episode commenced.

An individual with AFB smear-positive pulmonary TB is considered infectious starting three months prior to either the first positive smear or the onset of symptoms (whichever is earlier).

For AFB smear-negative TB, the infectious period is considered to begin one month prior to symptom onset.

This information is used to guide contact tracing efforts.

Steps in Contact Investigation

1.Identification of the Index Case
Confirm bacteriologically positive pulmonary TB and obtain details on infectious period and household structure.
2.Listing of Contacts
Prepare a list of all household and close contacts with demographic data, exposure history, and risk factors.
3.Clinical Screening
All contacts should be screened for TB symptoms (cough >2 weeks, fever, night sweats, weight loss, or failure to thrive in children).
4.Diagnostic Evaluation
a)Symptomatic contacts: Chest X-ray, sputum Xpert MTB/Rif and further tests as indicated.
b)Asymptomatic contacts (especially children and immunocompromised): Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA) for LTBI detection.
5.Management
- **Active TB disease:** Start appropriate treatment.
- **Latent TB infection (LTBI):** Offer TB preventive treatment (TPT), e.g. isoniazid (INH) for 6 months, or alternative regimens as per national guidelines.
- **No infection/disease:** Provide education and counsel on symptoms and follow-up if symptoms develop.

Summary table:

Step	Action	Tool/Test	Outcome
Identify	Index case	Confirmed pulmonary TB	Initiate investigation
Screen	All contacts	Symptom review	Identify presumptive TB
Diagnose	Symptomatic contacts	CXR, Xpert MTB/Rif	Active TB
Test	Asymptomatic, high-risk	TST/IGRA	LTBI
Manage	Based on result	TPT or TB treatment	Prevention/cure

References:

1.World Health Organization. WHO consolidated guidelines on tuberculosis: Module 5 – Management of tuberculosis preventive treatment. Geneva: World Health Organization; 2020.
2.World Health Organization. WHO operational handbook on tuberculosis: Module 5 – Tuberculosis preventive treatment. Geneva: World Health Organization; 2020.
3.National TB Control Program, Pakistan. National guidelines for the management of tuberculosis. Islamabad: National TB Control Program; 2022.
4.World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization; 2012.

Chapter 12:
Latent TB Infection (LTBI)

Definition and Epidemiological Importance of LTBI

LTBI is a state in which a person is infected with Mycobacterium tuberculosis but does not (yet) have clinically manifest active disease nor is infectious. The immune system mounts a persistent response, but the bacteria remain dormant or contained. The importance of LTBI lies in its potential to progress to active TB disease, particularly in high-risk individuals thus contributing to ongoing transmission and morbidity. The WHO emphasizes that programmatic management of LTBI is "a critical activity to disrupt Mycobacterium tuberculosis transmission".

In Pakistan's context, given the high TB incidence and crowded living conditions, identifying and treating LTBI among contacts and at-risk populations becomes a key component of the national control strategy. The NTP vision emphasises moving toward a TB-free Pakistan by 2030 with zero deaths, disease and poverty due to TB.

Risk-Groups For Progression From LTBI To Active Disease

Progression from LTBI to active disease is influenced by both host and environmental factors. Key risk groups include:

- Household contacts of active pulmonary TB cases
- People living with HIV or other immunosuppressive conditions
- Person with silicosis, chronic renal failure, diabetes, malnutrition or heavy alcohol/tobacco use
- Health care workers and people in congregate settings
- In high burden settings, person with recent infection.

WHO guidance stresses prioritising these high-risk groups for targeted testing and treatment of LTBI. In Pakistan, given resource constraints, a risk-based approach is pragmatic.

Identification and Testing of LTBI

Testing for LTBI typically uses immunologic assays such as the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs). WHO emphasises that countries should adopt a public-health approach based on epidemiology and resource availability.

In practice in Pakistan:

- For contacts of smear-positive TB patients, especially children and immuno-compromised, screening for LTBI should be considered.
- A systematic algorithm: exclude active TB disease first (via symptoms, chest X-ray, appropriate microbiology) before commencing LTBI treatment.
- In the absence of accessible IGRA or TST in some settings, risk-factor based decision-making may apply, recognising limitations.

Treatment of LTBI

Treatment of LTBI aims to prevent progression of active disease. The WHO consolidated LTBI guidelines provide evidence-based options. Key regimen options (in settings where drugs are available and susceptibility can be assumed) include:

- 3 months once-weekly isoniazid plus rifapentine
- 3–4 months daily isoniazid + rifampicin or rifampicin alone
- 6–9 months daily isoniazid monotherapy (less preferred due to longer duration and lower completion).

Completion rates, safety, drug-interaction profiles and programmatic feasibility must be considered. For Pakistan, the shorter rifamycin-based regimens may be more attractive, but drug availability, cost, interactions (especially in persons on other medications) and monitoring capability must be factored in.

Monitoring, Evaluation and Operational Considerations

For programme implementation, the following are critical:

- Ensuring active TB disease is excluded before LTBI treatment begins (to avoid monotherapy in active disease and risk of resistance).
- Monitoring for adverse events (particularly hepatotoxicity with isoniazid, drug interactions with rifamycin's).
- Ensuring adherence and completion of the LTBI regimen — programmatic factors such as counselling, follow-up, and recording are vital.
- Integration with the NTP's reporting systems to allow measurement of how many contacts were screened, treated, completed therapy.

References:

1.World Health Organization. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis preventive treatment. Geneva: WHO; 2020.
2.National TB Control Programme Pakistan. National Strategic Plan 2020–2023: Towards a TB-Free Pakistan. Islamabad: NTP; 2020.
3.Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69(RR-1):1–11.
4.World Health Organization. Global Tuberculosis Report 2024. Geneva: WHO; 2024.

Chapter 13:
Drug-Resistant TB (DR-TB)

Although the focus of this guideline is DSTB, an overview of DR-TB is important to assist GPs and consultants in recognizing when to refer and how to coordinate.

Word of Caution: It is recommended to avoid treating patients suspected/proven cases of DR-TB because the treatment of such cases need comprehensive package to diagnose, treatment and follow up. Beside drugs required to treat are not available in the open market and half-hearted treatment will lead to development of more drug resistance and pool of patients with total drug resistance which will be a public health hazard as they will spread DR-TB in the community that will lead to disaster. Such cases should be referred to Programmatic Management of Drug- Resistant Tuberculosis (PMDT) sites located in large cities of Pakistan (see List below). In each programmatic management of drug-resistant TB (PMDT) site proper facilities to diagnose, treat and follow up facilities are available.

Types of Drug-Resistant TB

DR-TB Classification	
Mono-drug resistant TB	Resistance to one first-line anti-TB drug only
Poly-drug resistant TB	Resistance to more than one first-line anti-TB drug, but not both isoniazid and rifampicin.
Multi-drug-resistant TB (MDR-TB)	Resistance to at least both isoniazid and rifampicin
Rifampicin-resistant TB (RR-TB)	Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs
Pre-XDR TB	MDR/RR TB and resistance to any fluoroquinolones (FQs)
Extensively-drug resistant TB (XDR-TB)	MDR/RR TB and resistance to any fluoroquinolones (FQs) and to at least one additional Group A drug (Bedaquiline & Linezolid)

Patients Who Are Most At Risk Of Having DR-TB

- Previously treated patients.
- Individuals with TB symptoms are contacts of patients with known RR-TB.
- Other groups – Immunocompromised (HIV), vulnerable disease, CXR suggestive of TB, Children below 15 years and patients with extra pulmonary TB.
- TB patients under Treatment who fail to convert at the end of intensive phase or subsequent follow up (both for New & previously treated)
- Smear Negative reported as smear- positive

Family Physicians / Health Care Providers Are Expected To:

- Identify MDR TB Presumptive
- Counsel the MDR TB Presumptive

- Refer MDR TB Presumptive for Gene Xperttesting(https://ntp.gov.pk/directory-of-tb-centers/) Have liaison with PMDT site to ensure patient enrolment
- Monitoring & management of minor side effects
- Support the patient when necessary for completion of treatment

MDR-TB management

- After DR-TB detection, enrolment proceedings are ensured
- Baseline investigations are requested and are free of cost
- An appropriate treatment supporter is identified for DOT
- Psycho-social assessment and psychological support is provided by trained psychologist at PMDT site
- One-month medicines are provided to the patient along with proper instructions that when and how to take the medicines
- Household visit is arranged by treatment coordinator
- Monthly follow up at PMDT site is arranged to monitor progress of treatment
- On monthly basis social support in the form an incentive of cash amount via easy paisa mobile phone account, is provided to the patients and treatment supporter after each Follow up visit.

Post-treatment Monitoring:

Post treatment monitoring should be performed once the treatment is completed every six months during the following two years. The assessment should include the following examination:

1. Sputum smear examination and culture (if sputum is available)
2. Body weight
3. Chest X-ray
4. DST (if culture result is positive)

As relapse of TB may occur in cured RR-TB patients, they should be instructed to consult the clinic if they experience TB specific signs and symptoms again. If the patient has stopped treatment before completing the recommended full treatment, the patient should be traced and assessed every 6 months for at least 2 years to detect signs and symptoms of TB, to do investigations and re-treatment if indicated.

Details of DR-TB sites - March 2025

No.	Province	District	Site Name
1	Azad Jammu & Kashmir (AJK)	Muzaffarabad	Abbas Institute of Medical Sciences (AIMS)
2		Mirpur	DHQ Mirpur
1	Balochistan	Loralai	DHQ Hospital, Loralai
2		Quetta	FJ Chest Hospital, Quetta
3		Hub	Jam Ghulam Qadir Hospital
4		Jaffarabad	DHQ Dera Allah yar
5		Kech (Turbat)	DHQ Turbat

6	Balochistan	Nushki	DHQ Hospital
7		Jhal Magsi	RHC
8		Usta Mohammad	DHQ Hospital
9		Khuzdar	Teaching hospital
10		Qilla Saifullah	DHQ Killa Saifullah
11		Qilla Abdullah	DHQ Abdul Rehman Zai
1	GB	Gilgit	Provincial Headquarter hospital, Gilgit
1	ICT	Islamabad	PIMS
1	KPK	Abbottabad	ATH Abbottabad
2		Peshawar	LRH Peshawar
3		D.I. Khan	MMMTH D.I. Khan
4		Swat	STH Swat
5		Mardan	MMC Mardan
6		Haripur	DHQ Haripur
7		Bannu	KGNTH Bannu
8		Nowshera	DHQ Nowshera
9		Charsadda	DHQ Charsadda
10		Shangla	DHQ Shangla
11		Buner	DHQ Buner
12		Hangu	DHQ Hangu
13		Kohat	DHQ Kohat
14		Lakki Marwat	DHQ Lakki Marwat
15		Dir Lower	DHQ Dir Lower
16		Malakand	DHQ Malakand
17		Mansehra	DHQ Mansehra
18		Chitral	DHQ Chitral
19		Swabi	DHQ Swabi
1	Punjab	Attock	DHQ Hospital
2		Bahawalpur	BV Hospital
3		Faisalabad	DHQ Hospital
4		Lahore	Mayo Hospital
5			Jinnah Hospital
6			Gulab Devi Hospital
7		Multan	Nishtar Hospital
8		Okara	DHQ Hospital
9		Rahimyar Khan	Sheikh Zayed Hospital
10		Rawalpindi	Samli Sanitorium Murree
11			Rawalpindi Leprosy Hospital
12			Military Hospital
13		Sargodha	DHQ Hospital

14		Sheikhupura	DHQ Hospital
15		Sialkot	AIM Hospital
16		Bahawalnagar	DHQ Hospital
17		Chakwal	DHQ Hospital
18		Gujranwala	DHQ Hospital
19		Jhang	DHQ Hospital
20		Kasur	DHQ Hospital
21		Khanewal	DHQ Hospital
22		Layyah	DHQ Hospital
23		Lodhran	DHQ Hospital
24		Mandi Bahauddin	DHQ Hospital
25		Mianwali	DHQ Hospital
26		Vehari	DHQ Hospital
1	Sindh	Badin	DHQ Hospital
2		Hyderabad	LUMHS Hyderabad
3		Jacobabad	DHQ Hospital
4		Jamshoro	ICD, Kotri
5		Karachi Malir	NCC -Karachi
6		Karachi-East	OICD, Hospital
7		Karachi-Korangi	Indus Hospital
8		Karachi-South	JPMC Hospital
9		Khairpur	TB Hospital
10		Larkana	CMC Hospital
11		Mirpurkhas	DHQ Hospital
12		Nawabshah (SBNB)	PMC Hospital
13		Qamber Shahdad Kot	DHQ Kambar Shahdadkot
14		Sanghar	DHQ Sanghar / CH Sanghar
15		Sukkur	GMM, Hospital
16		Tharparkar	DHQ Hospital, Mithi

References:

1.World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment - drug-resistant tuberculosis treatment. Geneva: WHO; 2020.
2.World Health Organization. Global Tuberculosis Report 2024. Geneva: WHO; 2024.
3.World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment and care for tuberculosis disease: drug-susceptible tuberculosis, tuberculosis HIV coinfection, and drug-resistant tuberculosis including tuberculosis preventive treatment. Geneva: World Health Organization; 2022.

Chapter 14:
Role of Family Physicians and Health-Care Providers in TB Control

Introduction

The success of TB control in Pakistan substantially depends on the engagement of family physicians (FPs) and front-line health-care providers (HCPs) — both in the public and private sectors. Given that a significant proportion of patients with TB first present to general practitioners or family physicians rather than designated TB-units, the role of these providers is critical.

Why Family Physicians and HCPs Matter in Pakistan

- **Early presentation:** Many TB patients in Pakistan first seek care from FPs/private practitioners rather than public TB labs or clinics.
- **Continuity of care:** FPs often provide longitudinal care (identification of risk factors, comorbidities, follow-up) which is vital for adherence and treatment success.
- A**ccess and trust:** FPs and primary HCPs often enjoy patient trust and have accessibility, allowing them to play a role in counselling, adherence support and early detection.
- **Integration with NTP:** The NTP emphasizes public-private mix (PPM) approaches for universal access to quality TB care. FPs must align with the national system for notification, standard treatment regimens and monitoring.

Key Responsibilities of FPs/HCPs in DSTB Management

Case Finding & Suspicion

- Maintain a high index of suspicion in patients with cough >2 weeks, weight loss, night sweats, fever, especially in high-risk groups (contacts of TB, diabetes, HIV, malnutrition).
- Use appropriate initial investigations (sputum smear, X-pert MTB/RIF, chest X-ray) consistent with national algorithms.
- Recognize risk of DR-TB: prior TB treatment, contact with known DR-TB case, persistent positive sputum after initial months of therapy.

Diagnosis and Referral

- Once suspicion arises, promptly refer for diagnosis through NTP-certified labs or public/private PPM labs.
- For DSTB: ensure baseline investigations (smear, Xpert, culture if available, chest imaging, assessment of comorbidities).
- Communicate with NTP TB-unit or chest-clinic for coordination of care.
- Notify the case: FPs must ensure that the newly diagnosed TB case is notified to the NTP (as per national requirements).

Initiation of Treatment and Adherence Support

- Use standard first-line DSTB regimen as per NTP/PCS guideline (e.g., 2RHZE/4RH).
- Educate the patient and family about TB disease, importance of adherence, potential side-effects, and the public-health importance of completing treatment.

- Establish a treatment plan: which provider will dispense drugs, how will follow-up visits be scheduled, how will adherence be monitored (pill cards, DOT where feasible, SMS reminders, etc.).
- Identify and manage comorbidities (diabetes, HIV, malnutrition, smoking cessation) which impact TB outcomes.

Monitoring Treatment Response & Side-effects

- Monthly review of symptoms, weight gain, sputum conversion.
- Monitor adverse events: hepatotoxicity, rash, neuropathy, visual changes, drug-interactions (e.g., rifampicin with antidiabetics, warfarin, antiretrovirals).
- Liaise with TB-unit if delayed sputum conversion, treatment interruption, adverse events, or suspected drug-resistance arises.
- Support nutritional counselling, smoking cessation, and psychosocial support if required.

Treatment Completion and Post-treatment Follow-up

- Confirm treatment completion and document end-of-treatment outcome (cured, treatment completed).
- After completion, counsel patients regarding the low but present risk of relapse, and advise prompt presentation if TB symptoms recur.
- Ensure integration with NTP's monitoring database and ensure the patient is reported in the national outcome data.

Prevention, Contact Investigation and LTBI Considerations

- On diagnosing a TB case, initiate contact tracing: identify household contacts and high-risk contacts (children <5 years, immunocompromised).
- Offer screening for active TB among contacts; for LTBI among high-risk contacts and implement preventive therapy as discussed in this guideline.
- Educate the family and community about cough hygiene, ventilation, respiratory etiquette, and the non-infective nature of LTBI (though caution needed until active disease excluded).

Practical Algorithm for the FP/HCP in Pakistan

1.Patients present with symptoms suggestive of TB take detailed history (duration, symptoms, risk-factors).
2.If suspicion high → order investigations (sputum smear, Xpert, chest X-ray) or refer to certified lab.
3.If active TB confirmed register with NTP, inform TB-unit, initiate standard DSTB regimen, counsel patient & family, plan adherence support
4.If using private sector, ensure coordination with NTP programme (notification, drug supply, follow-up).
5.Monitor monthly: symptoms, side-effects, adherence; refer early if non-conversion at 2 months or if side-effects arise.
6.On completion of treatment document outcome, counsel, follow-up as required.

7.Conduct contact investigation: identify household contacts, screen for active disease; if it is high risk and no active disease, consider LTBI management as discussed in this guideline.
8.Maintain proper documentation, notify as per NTP policy, coordinate with TB-unit for data entry and programme feedback.