NATIONAL TB GUIDELINES

2024

National Guidelines
TB Case Management
2024

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Executive Summary

The National TB Management Guidelines 2024 aim to provide a comprehensive reference for health care professionals involved in TB control activities in Pakistan. The guidelines outline the key components of the National TB Control Program and standardize the protocols for diagnosing and treating TB patients.

The guidelines are designed to enhance the effectiveness of TB control efforts in the country, which faces a significant burden of the disease. Pakistan ranks fifth among the high-burden TB countries globally, with an estimated 686,000 new cases and 15,000 drug-resistant TB cases emerging each year.

By providing a unified, evidence-based framework, the National TB Management Guidelines 2024 aim to support health care professionals in delivering high-quality, equitable TB care and contribute to the country's goal of achieving a TB-free Pakistan by 2030.

Prompt and accurate diagnosis, along with effective treatment, are essential not only for providing good patient care but also for playing a key role in the public health response to tuberculosis. All health care providers treating tuberculosis patients have a responsibility to both the individual and the community as a whole. The National Guidelines incorporate WHO definitions and treatment protocols for TB, aligned with "International Standards" for Tuberculosis Care, to address drug-resistant TB and ensure high-quality care for all patients, including those with different types of TB and HIV infections.

National Guidelines has been organized to address all the essential TB control program components. The guideline provides the most up-to-date information of TB epidemiology in Pakistan and strategies to control the disease in coming years. In addition to new definitions, the guidelines also include the most up- date National recommendation on TB treatment regimen for adults, children and for DR-TB cases. The new sections and chapters included in the guideline provide information on TB Screening, TB Preventive Treatment and TB and Comorbidities TB control program management, capacity building, infection control, monitoring and evaluation.

Foreword

The National TB Control Program in Pakistan aims to make the country TB-free by 2035 by providing free of cost high quality TB diagnosis and treatment.

The National TB Control Program Pakistan along with Provincial TB Control Programs and collaborative stakeholders, has developed revised guidelines to align it with new World Health Organization (WHO) recommendations. These comprehensive guidelines encompass all facets of TB treatment and care, consolidated into a single document for health care professionals. Key areas addressed include TB screening, diagnosis, and treatment for adults, adolescents and children including DRTB management and TB Preventive Treatment. The intended recipients encompass doctors, nurses, pharmacists, laboratory technologists, and program management personnel engaged in TB patient care. The developmental process entailed substantial efforts by national and provincial technical teams, WHO, and collaborative partners, incorporating national consultations and insights from experts and implementers.

The final document underwent meticulous review, aiming to improve knowledge on new TB recommendations and facilitate the rapid expansion of comprehensive and quality TB services throughout Pakistan.

I thank all the technical partners and donors for their support in developing this document. I am confident that these guidelines will help health care providers for comprehensive TB management. Together we continue the struggle to End TB.

Dr. Qasim Abbas
National Coordinator
Common Management Unit

Acknowledgement

The National TB guidelines is a revision and update of the TB Guidelines in accordance to new WHO recommendations. These guidelines include TB screening, diagnosis, and treatment for adults, adolescents and children including DRTB management and TB Preventive Treatment.

We are thankful to the valuable and meaningful support of USAID for their financial and technical support in developing and reviewing these guidelines. We are also thankful to our technical partners specially WHO for their continuous guidance. We acknowledge the kind support of Provincial TB Control Programs of Punjab, Sindh, Khyber-Pakhtunkhwa and Balochistan for their continuous support.

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Acronyms

ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
ART	Anti-Retroviral Treatment
ATT	Anti-Tuberculosis Treatment
B+	Bacteriologically Positive
CNSTB	Central Nervous System Tuberculosis
CALHIV	children and adolescents living with HIV
CHTB	Childhood TB
DHO	District Health Officer
DHQ	District Headquarter Hospital
DLS	District Laboratory Supervisor
DOTS	Directly Observed Treatment (short Course)
DRTB	Drug Resistant TB
DRS	Drug Resistance Survey
DST	Drug Sensitivity Testing
DTC	District TB Coordinator
EPTB	Extra Pulmonary TB
FLD	First Line Drug
FL-LPAs	First-line LPAs
GF	Global Fund
GP	General Practitioner
GUTB	Genitourinary TB
HH Contacts	Household Contacts
HIV	Human Immunodeficiency Syndrome
IDPs	Internally Displaced Persons
IEC	Information, Education and Communication
IGRAs	Interferon Gamma Release Assays
INH	Isoniazid
IPT	INH Prophylaxis Therapy
LPA	Line Probe Assay
LTBI	Latent TB Infection
M&E	Monitoring and Evaluation
MDR-TB	Multi Drug Resistant Tuberculosis
MO	Medical Officer
MTBC	Mycobacterium Tuberculosis
NGOs	Non-government Organizations
NSP	National Strategic Plan

NTP	National Tuberculosis Control Program
OATB	Osteoarticular Tuberculosis
PLHIV	People Living with HIV
PMDT	Programmatic Management of Drug-Resistant TB
PPD	Purified Protein Derivative
PPM	Public Private Mix
PRL	Provincial Reference Laboratory
PTB	Pulmonary TB
PTP	Provincial Tuberculosis Control Program
RR-TB	Rifampicin-resistant TB
TB	Tuberculosis
TCHs	Tertiary Care Hospitals
THQ	Tehsil Headquarter Hospital
TST	Tuberculin Skin Testing
WHO	World Health Organization
WRD	WHO-approved Rapid Diagnostics
XDR-TB	Extensively Drug-resistant TB

Case Definitions (As per WHO's latest surveillance guidelines)

Prevention of and screening for TB disease

Term	Definition
Contact person	Any person who was exposed to a person with TB.
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. [a]
Contact investigation (or evaluation)	A systematic process for identifying previously undiagnosed people with TB among the contacts of an index case. Contact investigation consists of identification, prioritization and clinical evaluation. It may also include testing for TB infection to identify candidates for TB preventive treatment.
Household contact	A person who has shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods in the 3 months before TB disease was identified in the index case.
Index patient (index case) of TB	The initially identified person with TB disease in a specific household or other comparable setting in which others may have been exposed. An index patient is the person on whom a contact investigation is centered but who is not necessarily the original source of an outbreak of TB.
Patient-initiated care	A patient-initiated pathway to TB diagnosis involves: (1) a person with TB disease experiencing symptoms that they recognize as serious; (2) the person having access to and seeking care, and presenting spontaneously at an appropriate health facility; (3) a health worker correctly assessing that the person fulfills the criteria for presumptive TB; and (4) the successful use of a diagnostic algorithm with sufficient sensitivity and specificity to diagnose TB.
Person with presumptive TB	A person with symptoms or signs suggestive of TB disease.
Provider-initiated care	Screening and testing initiated by health care providers. This can be done in health facilities or communities by mobile teams, often using mobile X-ray and rapid molecular tests.
Risk groups	Any group of people at increased risk of TB infection, or progression from TB infection to TB disease, or TB-associated mortality, compared with the general population.

Screening	The systematic identification of people at risk for TB disease in a predetermined target group by clinical examination, assessing symptoms and using tests (sputum-smear microscopy, LF-LAM, C-reactive protein), or other procedures (e.g. chest radiography). For those who screen positive, diagnosis should be established by one or more diagnostic tests (e.g. mWRD, culture). This term is sometimes used interchangeably with "active tuberculosis case-finding". It should be distinguished from testing for TB infection (using a TB skin test or interferon-gamma release assay).
TB infection	A state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of the clinical manifestations of TB disease. This is also at times referred to as "latent TB infection". There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no signs or symptoms of TB but are at risk for progression to active TB disease.
TB preventive treatment (TPT)	Treatment offered to individuals who are considered at risk of progression from TB infection to TB disease. Also referred to as treatment of TB infection, treatment for latent TB infection or TB preventive therapy.

[a] Commencement of disease may be dated to the onset of first signs or symptoms.

Diagnosis of TB disease

A person with TB disease

Term	Definition
TB disease	A person with disease caused by the *M. tuberculosis* complex. Note: The *M. tuberculosis* complex comprises nine distinct but closely-related organisms. The complex includes *M. africanum, M. bovis, M. canetti, M. caprae, M. microti, M. mungi, M. orygis, M. pinnipedii,* and *M. tuberculosis*.
TB case	The occurrence of TB disease in a person. *The term should be reserved for use in the context of registration or reporting of the clinical condition and not during the provision of care*. This definition also includes the identification of TB disease through post-mortem examination. 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).
TB patient	A person who is receiving care for TB disease.

Classification of a person with TB disease by method of diagnosis

Term	Definition
Bacteriologically confirmed	A person from whom a biological specimen is positive by a WHO-recommended rapid diagnostic test, culture, or smear microscopy.
WHO-recommended rapid diagnostic test (WRD)	A test approved by WHO that employs molecular (e.g. Xpert Ultra®) or biomarker-based techniques (e.g. urinary lipoarabinomannan assays (U-LAM)) for the diagnosis of TB. Throughout this publication, the term "WRD" refers to molecular WRDs unless otherwise specified.
Clinically diagnosed	A person who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment. This definition includes pulmonary cases diagnosed based on radiographic abnormalities and extrapulmonary cases diagnosed based on suggestive clinical presentation or histology. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Classification of a person with TB disease by anatomical site

Term	Definition
Pulmonary TB	A person with TB disease involving the lung parenchyma or the tracheobronchial tree. Note: A case with both pulmonary and extrapulmonary TB should be recorded and counted as a pulmonary TB case for surveillance purposes. Milliary TB is classified as pulmonary TB.
Extrapulmonary TB	A person with TB disease involving organs other than the lung parenchyma or tracheobronchial tree (e.g. pleura, lymph nodes, digestive tract, genitourinary tract, skin, joints and bones, meninges).

Classification of a person with TB disease by history of previous treatment for TB

Term	Definition
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.

	Note: Examples of re-registered cases include: • a person who was declared *treatment failed* during or at the end of their most recent course of TB treatment and who is starting a new course of TB treatment (normally using a different drug regimen); • a person who was declared *lost to follow-up* before, during or at the end of their most recent course of TB treatment and who has returned to start a new course of TB treatment; and • a person whose outcome after their most recent course of TB treatment is undocumented and who has returned to start 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 of a person with TB disease by susceptibility or resistance to TB medicines (not mutually exclusive)

Term	Definition
Drug susceptibility testing (DST)	In vitro testing of a strain of *M. tuberculosis* complex using either: 1) molecular, genotypic techniques to detect resistance-conferring mutations; or 2) phenotypic methods to determine susceptibility to a medicine.
Drug-resistant TB (DR-TB)	A person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to any TB medicines tested. When available, DST results for individual drugs should be recorded.
Drug-susceptible TB (DS-TB)	A person with TB disease for whom there is no evidence of infection with a strain of *M. tuberculosis* complex that is resistant to rifampicin or isoniazid. This includes people for whom DST was not done or for whom DST shows a strain of *M. tuberculosis* complex that is susceptible to both rifampicin and isoniazid. This definition should only be used for the purposes of initiation of treatment for drug-susceptible TB and the recording of treatment outcomes. Wherever available, DST results for individual drugs should be recorded and used to define a person's drug

	susceptibility status. When DST results are not available for individual drugs, their absence should also be recorded.
Isoniazid-resistant, rifampicin-susceptible TB (Hr-TB)	A person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.
Rifampicin-resistant TB (RR-TB)	A person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be either susceptible or resistant to isoniazid (i.e. MDR-TB) or resistant to other first-line or second-line TB medicines.
Multidrug-resistant TB (MDR-TB)	A person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to both rifampicin and isoniazid.
MDR/RR-TB	MDR-TB is a subset of RR-TB, and the two are often grouped together using the term MDR/RR-TB.
Pre-extensively drug-resistant TB (pre-XDR-TB)	A person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to rifampicin (and which may also be resistant to isoniazid), and which is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).
Extensively drug-resistant TB (XDR-TB)	A person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to rifampicin (and which may also be resistant to isoniazid) as well as resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and at least one other "Group A" drug (Bedaquiline or Linezolid) *(10)*.

Classification of a person with TB disease by HIV status

Term	Definition
HIV-positive	A person with TB disease who has a documented positive result from HIV testing before, at the time of TB diagnosis or during the TB episode.
HIV-negative	A person with TB disease who has a negative result from HIV testing conducted at the time of TB diagnosis. Note: If the person is subsequently found to be HIV-positive during their TB treatment, they should be reclassified as an HIV-positive TB case.
HIV status unknown	A person with TB disease who has no result from HIV testing and no documented evidence of receiving treatment for HIV. Note: If the person's HIV status is subsequently determined, they should be reclassified as an HIV-positive TB case or an HIV-negative TB case, as appropriate.

Treatment for TB disease

The terms in the table below cover the period from initiation to completion of treatment for people diagnosed with TB disease.

Treatment types and treatment initiation

Term	Definition
First-line TB medicine (or drug)	An agent used to treat a person with drug-susceptible TB disease.[a]
Second-line TB medicine (or drug)	An agent used to treat a person with drug-resistant TB disease.[b]
Treatment initiation	The initiation of an appropriate treatment regimen for a person with TB disease. Note: It is recommended to monitor this step in the pathway of care because diagnosis of TB disease does not necessarily mean that a person will be offered or accept to take treatment.

[a] First-line treatment regimens comprise combinations of the following drugs: isoniazid, rifampicin, ethambutol, pyrazinamide, rifabutin, rifapentine, moxifloxacin.

[b] Second-line treatment regimens comprise combinations of the following drugs: *Group A*: levofloxacin or moxifloxacin, bedaquiline, linezolid. *Group B*: clofazimine, cycloserine or terizidone. *Group C* (when Group A and Group B cannot be used): ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin, ethionamide or prothionamide, *p*-aminosalicylic acid.

Treatment Outcomes for TB disease

Case and treatment outcomes for both drug-susceptible and drug-resistant TB

Term	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response[a] and no evidence of failure.
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 person with TB disease whose treatment regimen needed to be terminated or permanently changed[b] to a new regimen option or treatment strategy.
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.

[a] In this context, a **bacteriological response** is defined as a bacteriological conversion with no reversion. A **bacteriological conversion** occurs when a patient with bacteriologically confirmed TB has at least two consecutive negative cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart. **Bacteriological reversion** occurs when a patient with bacteriologically confirmed TB has at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, which are positive either after a bacteriological conversion or in patients without bacteriological confirmation of TB.

[b] Reasons for regimen change may include no clinical response and/or no bacteriological response, an adverse drug reaction or evidence of additional drug resistance to medicines in the regimen.

Chapter 1

Introduction

1. Introduction

1.1. Basics about Tuberculosis

Tuberculosis (TB) is one of the oldest diseases known to affect humans and studies of human skeletons have shown that it has affected humans for thousands of years. While lungs are most commonly affected by TB, pulmonary tuberculosis (PTB) is the most common presentation. TB can involve every organ system.

1.1.1. Pathogen and pathogenesis of Tuberculosis

Causative Organism of Tuberculosis

Tuberculosis is caused by a group of closely related bacteria, collectively known as the *Mycobacterium Tuberculosis complex* (MTBC) *that* causes TB in humans and animals. Worldwide TB in humans is mainly caused by *M. Tuberculosis* resulting in high mortality and morbidity *M. Africanum* causes human TB but is restricted to West Africa, where it accounts for up to 50% of cases. *M. Canettii* is an extremely rare cause of human TB in the Horn of Eastern Africa. Whereas *M. Bovis* an animal-adopted strain, causes disease in cattle and spreads to humans through animal contact and consumption of unpasteurized milk. Other disease-causing species of MTBC are animal-adapted strains that range across different mammalian species. *M. Tuberculosis* and *M. Africanum* are obligate human pathogens with limited survival outside the human body and no known animal reservoir.

M. tuberculosis, the causative organism of tuberculosis, was discovered in 1882 by Dr Robert Koch, ***M. Tuberculosis*** (TB) are slightly curved, rod-shaped bacilli, 0.2-0.5 microns in diameter; 2-4 microns in length, have a thick lipid (mycolic acid) cell wall and once stained resists decolorization with acid/alcohol and therefore called Acid Fast bacilli. M.TB is aerobic, non-motile, and multiplies slowly (~ every 18- 24 hours), and metabolism can slow to the point of dormancy and can remain in this state for decades.

1.1.2. TB transmission

TB transmission usually takes place through the airborne spread of droplet nuclei. The disease is spread when people sick with TB, expel bacteria into the air by coughing. When a person inhales droplet nucleus containing *M. Tuberculosis*, it passes through the upper respiratory tract and bronchi to reach the alveoli of the lungs.

Immune responses and outcomes of M. tuberculosis transmission

The immune response in TB is complex. In the first encounter between the immune system and *M. tuberculosis*, the effectiveness of the innate immune response dictates the clinical outcome. If the innate immune response is strong enough and the bacillary load is low, the bacteria are likely to be eradicated. Otherwise, *M. Tuberculosis* is confined to the host cells, leading to infection. At this point, the adaptive immune response determines the progress of the disease from an active to a progressive one. On average, only 5-10% of those who are infected develop active TB disease during their lifetime, with 3 to 5% developing TB in the first year following infection and an additional 3 to 5% any time after the first year. Longitudinal studies have shown that the majority of TB disease

manifests soon after infection and rarely occurs more than two years after infection. The vast burden of global TB is, therefore, from recently transmitted infection.

TB disease entity

M. Tuberculosis produces two distinct disease entities known as primary and post-primary TB.

Primary TB occurs in immune-competent people when infected with *M. Tuberculosis* for the first time. Primary TB typically develops and spreads to regional lymph nodes and then systemically for only a few weeks before regressing as immunity develops. While the lesions may heal, they are seldom sterilized, and organisms persist. A primary (Ghon's) complex is formed, consisting of a granuloma, typically in the middle or lower zones of the lung (primary or Ghon's focus) in combination with transient hilar and/or paratracheal lymphadenopathy and some overlying pleural reaction. The primary complex usually resolves within weeks or months, leaving signs of fibrosis and calcification detectable on chest X-ray.

The symptoms are mild, non-specific, and usually self-resolving. In general, the risk of disease progression is low other than in very young or immunosuppressed individuals and those using TNF-suppressing agents. Infants (<2 years of age) are at the highest risk of disease development and potential dissemination. Hematogenous dissemination of bacilli may occur shortly after primary infection or from any active disease site and may result in Milliary TB. Milliary granulomas are 1–3 mm in diameter (the size of a millet seed), are widespread, and may be found in any visceral organ.

Post-primary TB, also known as adult-type or secondary TB, occurs in people who have developed immunity to primary TB. Post-primary TB is typically restricted to the upper lobes of the lungs and does not involve lymph nodes or other organs. About 90% of cases recover spontaneously without therapy. However, those who become ill account for 80% of all clinical cases and nearly 100% of transmission of infection. Lung cavitation and transmission is likely dependent on a robust immune response as elderly people and those infected with HIV tend to develop more disseminated disease with less cavitation.

Risk Factors: The risk of progression from exposure to *M. tuberculosis* bacilli to the development of active disease is governed by both exogenous and endogenous risk factors. Exogenous factors like bacillary load in the sputum and an individual's proximity to an infectious TB patient play a key role. Endogenous risk factors and comorbidities such as HIV infection, diabetes, malnutrition, and tobacco and substance use disorders increase the risk of contracting TB and are associated with poorer TB treatment outcomes.

1.1.3. Mechanism of Drug-Resistance in TB

Members of the genus Mycobacterium have long been noted for their intrinsic resistance to a wide array of antibiotics. Most of the drug resistance in clinical *M. Tuberculosis strains* is attributed to chromosomal mutations in existing genes that are passed along from mother to daughter cells through vertical descent. Unlike many other bacterial pathogens, *M. Tuberculosis rarely* recombines via lateral DNA exchange and also *lacks* plasmids. Resistance could be present either at the onset of the disease because of the transmission of drug-resistant strains (primary drug resistance] or might emerge during the disease due to inadequate treatment (acquired drug resistance).

1.2. Clinical Manifestations of TB

Following inhalation of *M. Tuberculosis,* an individual may have one of the following outcomes: i) fail to register an infection ii) become infected but then clear the infection, iii) successfully contain the infection but continue to harbor bacilli in the absence of symptomatic disease (LTBI), or iv) develop progressive TB disease. Most infections manifest as a clinically asymptomatic, contained state; a smaller subset of infected individuals present with symptomatic active TB.

"Tuberculosis (TB) infection is a condition characterized by a persistent immune response to stimulation by *M. Tuberculosis* antigens, without any evidence of active TB. Most infected individuals show no signs or symptoms of TB, but they are at risk of developing active TB and may become contagious. On average, 5 to 10% of those with TB infection will develop active TB at some point in their lives, with half of them developing the disease within the first two years of infection. The risk of developing active TB depends on several factors, the most important being the individual's immunological status."

Asymptomatic TB (Subclinical TB Cases)[1]: Active TB, at times, may be subclinical without symptoms with a risk of being missed in diagnosis. It is often reported in disease prevalence surveys in which all patients undergo both symptom and X-ray screening that a significant number of bacteriologically confirmed TB cases had no complaints of any symptoms and were investigated based on X-ray abnormalities the evidence from the prevalence survey[2]. Pulmonary Tuberculosis (PTB)

The lung is the predominant site of infection with *M. Tuberculosis*. This may result in symptomatic, primary PTB disease, usually in children or it may develop as post-primary PTB in adults. However, owing to the changing epidemiology, there is a considerable overlap in the radiologic presentations of these entities.

PTB in most cases, presents as a disease of the lung parenchyma and much less frequently as a disease of the tracheobronchial tree only. The classic clinical features of **parenchymal PTB disease** are chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, and hemoptysis. A persistent, non-remitting cough is the most frequently reported symptom. TB symptoms are usually gradual in onset; however, in young children or immunocompromised individuals, it may have an acute onset. On rare occasions, patients with sub-pleural involvement may present with symptoms of chest pain and dyspnea. Chest X-ray findings are often typical with focal, diffuse, or reticulonodular opacities in the upper lobe, consolidation, cavities, nodules, miliary pattern, intrathoracic lymphadenopathy, and pleural effusion. People presenting with any of these symptoms and/or a history of contact with infectious TB and/or abnormal chest radiographs raise suspicion of disease.

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[1] Agbota, G.; Bonnet, M.; Lienhardt, C. Management of Tuberculosis Infection: Current Situation, Recent Developments and Operational Challenges. Pathogens 2023, 12, 362. https://doi.org/10.3390/pathogens12030362

[2] Qadeer E, Fatima R, Yaqoob A, Tahseen S, Haq MU, Ghafoor A, et al. Population Based National Tuberculosis Prevalence Survey among Adults (>15 Years) in Pakistan, 2010–2011. PLoS One [Internet]. 2016 [cited 2019 Feb 4];11(2). Available from: http://ntp.gov.pk/uploads/Pakistan_TB_Prevalence_Survey_PLOS.pdf

Symptoms of **Endobronchial TB** affecting the trachea and major bronchi are like those of parenchymal PTB, but wheezing and dyspnea are often more prominent on examination. Some patients may present with normal chest X-rays.

1.2.1. Extrapulmonary Tuberculosis (EPTB)

M. Tuberculosis may spread directly from the lungs through the lymphatic system or bloodstream to other body sites at the time of initial infection, reactivation, or reinfection (post-primary TB), thereby causing extrapulmonary manifestations. Extrapulmonary involvement may present many years after exposure. TB can involve organs other than the lungs, e.g., pleura, lymph nodes, and meninges, abdomen, joints, bones, genitourinary tract, and skin.

Intra-thoracic lymph nodes form part of the primary (Ghon's) complex are typically seen in young children. Peri-hilar and/or paratracheal lymph node enlargement with or without airway compression is the cardinal sign of disease. Symptoms are similar to other forms of PTB, but productive cough and hemoptysis are rare. Diagnosis is complicated as the disease is often paucibacillary and young children are unable to expectorate. Enlarged lymph nodes may obstruct large airways, resulting in the collapse or hyperinflation of distal lung segments. Cold abscesses may form that may erode into surrounding structures like in the pericardium, esophagus, or airways, leading respectively to TB pericarditis, esophageal TB, or lobar consolidation and caseating pneumonia.

Extra-thoracic lymph node TB (LNTB): Extra-thoracic TB lymphadenitis is one of the most common forms of EPTB. More than 40% of LNTB patients have radiological evidence of PTB suggesting the lymphatic spread of *M. Tuberculosis* from the parenchyma of the lung. *M. Bovis*, was considered the more likely causative agent before the advent of pasteurization of milk. The most commonly affected lymph nodes are in the cervical region. The disease is indolent and usually presents as a unilateral painless neck mass at times with fistula or sinus formation, or cold abscess. Constitutional symptoms are rare, except in individuals infected with HIV. Tenderness or pain is often associated with secondary bacterial infection.

Pleural TB: TB is the leading cause of pleural effusions in TB-endemic countries. TB pleural effusion (TPE) is usually unilateral and variable in size. Concurrent parenchymal involvement is seen in 20 % of patients on chest X-rays and up to 80 % on CT scans. The typical presentation is acute with fever, cough, and localized pleuritic chest pain. TPE, when part of a primary infection, is often self-limiting but is often associated with occult dissemination in pregnancy with potential risk to the fetus. As with all forms of EPTB, the incidence is higher in HIV-infected patients with atypical symptoms, often with less pain, longer duration of illness, and more generalized signs. Previously, TPE was considered a delayed hypersensitivity reaction rather than a direct infection of the pleural space by *M. tuberculosis*. TB should be included in the differential diagnosis list of any undiagnosed pleural effusion.

Gastrointestinal tuberculosis (GITB). Abdominal TB can occur due to ingestion of bacilli from swallowed sputum or infected milk, hematogenous spread, local extension from contiguous mediastinal lymph nodes to the esophagus, or spread from the gut or nodes to the peritoneum. GITB is commonly seen in populations with lower socioeconomic status, illiteracy, malnutrition, and HIV.

The gastrointestinal tract can be involved anywhere along its length. The ileocecal area is the most common site and findings on imaging are described as ulcerative, hypertrophic, ulcero-hypertrophic, or fibrotic. Proximal GIT is rarely involved. Diagnosis of abdominal TB is often delayed as the clinical presentation is non-specific and two-thirds of these patients have normal chest X-rays.

Central Nervous System Tuberculosis (CNSTB) Hematogenous spread leads to a tuberculous focus (Rich focus) in the brain, invading and releasing bacilli in the subarachnoid space. In young children and HIV-infected patients, it is often associated with Milliary disease. The most common clinical manifestation of CNS-TB is Tuberculous meningitis (TBM) followed by CNS tuberculoma. Early symptoms are non-specific, including a triad of fever, night sweats, weight loss, and headache of increasing intensity. Neck rigidity is typically less pronounced than in acute bacterial meningitis. TBM is the most lethal form of TB. Almost a third of HIV-uninfected patients and more than half of patients co-infected with HIV die from TBM, and despite treatment, half of the survivors suffer from permanent neurological impairment.

Osteoarticular Tuberculosis (OATB): OATB results from hematogenous spread with a predilection for the spine and growing ends of long bones. The infection usually remains dormant for 3-4 years before clinical disease. The spine is the most common site and bacilli target the red bone marrow resulting in the gradual destruction of the bony tissue. The most common initial symptom of spinal TB is back pain, which may be present for weeks or months before diagnosis. An insidious, progressive back pain raises suspicion of tuberculous spinal infections. Once the vertebral integrity is lost, the structure collapses, and angulation (kyphosis) of the spine develops, which is sometimes followed by the fusion of vertebrae (ankylosis). Cold abscess formation or severe spinal angulation may cause compression of the spinal cord with neurological sequelae. A paraspinal abscess can appear as a mass or psoas abscess that discharges in the groin.

Genito-urinary Tuberculosis (GUTB); GUTB usually results from the reactivation of old, dormant tuberculosis diseases. The clinical presentation may vary from asymptomatic to non-specific constitutional symptoms. Depending on the disease site, the patient may present with abdominal pain, abdominal mass, menstrual irregularities, infertility, obstructive uropathy, and abnormal renal function tests. Kidneys are most frequently affected, and patients with renal TB have complaints of recurrent urinary tract infections and sterile pyuria, which does not respond to standard antibiotic therapy. GUTB is often diagnosed late owing to insidious onset and delay in diagnosis may result in disease progression and irreversible damage.

Rare clinical manifestations of EPTB; Other body sites are rarely affected and the patient may present with unusual manifestations intricating the diagnosis. Atypical manifestations of EPTB include swollen lips, severe pancytopenia due to the involvement of bone marrow, pain in the elbow, keratitis, lupus vulgaris resulting in loss of vision and nose.

Table 1: ***Extrapulmonary TB site and its specific symptoms***

	EPTB Disease SITE	Specific symptoms
1	Lymph nodes-(Extra-thoracic)	Swollen, matted lymph nodes. occasionally with pus discharge
2	Lymph node –Intra thoracic	Broadening of mediastinum, hilar shadows
3	Central Nervous system	In case of TB meningitis- headache, fever, neck stiffness and mental confusion
4	Osteo articular – Spine	Loss of function in lower limbs when there is gibbous and spinal involvement
5	Osteo articular – Other than Spine	Pain and swelling when joints are involved
6	Peritoneal/Intra-abdominal	Intestinal TB abdominal pain, anemia. Patients may present with symptoms of obstruction, right iliac fossa pain, or mass in the right iliac fossa
7	Pleural	Pleural effusion (dry cough, shortness of breath, heaviness on the side)
8	Genito urinary	Infertility in case of reproductive tract. Symptoms of urinary tract infection in case of genitourinary involvement
9	Milliary /Multiple	Milliary TB is the widespread dissemination of Mycobacterium tuberculosis via hematogenous spread, seeding of TB bacilli in the lung, as evidenced on chest radiography.
10	Other	Rare form of TB, eye, skin

1.3. Global burden of Tuberculosis (Global TB Report 2023)

About a quarter (2 billion) of the global population is estimated to be infected with *M. Tuberculosis*. Every year an estimated 10 million (range, 8.9–11.0 million) people fall ill with TB. Incidence rates at the national level vary from less than 5 to more than 500 per 100K population per year. TB can affect anyone anywhere, but most people who develop the disease (about 90%) are adults; (adult men accounted for 56%, women for 36%, and children for 8% of all TB patients notified in 2022). Among all TB cases, 7.3% were among people living with HIV.

TB is a prototypical disease of poverty. Despite causing up to half of all human deaths in Europe and North America over the past few centuries, TB today primarily affects the developing world. An inverse linear association is demonstrated between TB incidence and per capita gross domestic product (GDP). Thirty high TB burden countries (HBC) account for almost 86% of the global burden and two third of the total burden is born by eight countries including India (26%), China (8.5%), Indonesia (8.4%), Philippines (6.0%), Pakistan (5.8%), Nigeria (4.6), Bangladesh (3.6%) and South Africa (3.3%). This distribution predominantly tracks socio-economic status, with sub-Saharan Africa being one of the most intensely affected areas.

Extrapulmonary tuberculosis (EPTB*)* The proportion of Extra pulmonary TB among TB cases varies depending on the country of origin and associated human immunodeficiency virus (HIV) coinfection.

There were about 1.1 million TB deaths among HIV-negative people and an additional 0.17 million deaths among HIV-positive people, which is more than any other infectious disease. The only exception was during 2020-21 when a higher number of people died due to COVID-19 than TB.

1.3.1. Burden of Drug resistant TB

Nearly half a million individuals who developed tuberculosis have rifampicin resistance (RR), a key first-line drug for the treatment of tuberculosis. The highest proportions (>50% in previously treated cases) of drug resistance are reported in countries of the former Soviet Union. For more than 10 years, estimates of the proportion of people diagnosed for the first time with Multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB) has remained at about 3–4% and for those previously treated for TB has stayed at about 18–21%. This indicates that a substantive burden of drug-resistant TB is driven by ongoing transmission. Globally, 20.1% (95% CI: 15.5-25.0%) of MDR/RR-TB cases are resistant to fluoroquinolone (FQ), a core drug used to treat drug-resistant tuberculosis.

Among R-sensitive TB, the prevalence of H resistance is estimated at 7.4% (95% CI 6.5%–8.4%) among new and 11.4% (95% CI 9.4%–13.4%) among previously treated TB patients.

1.3.2. Global plans and strategies to end TB

The WHO in 1993, declared TB 'a global emergency' with deaths from TB higher than any previous year in history. Starting with the Global Plan to Stop TB 2001-2005 there have been at least three other global plans. Although progress was made overall these plans failed to reach and treat enough people with TB to make a success of the plan.

End TB Strategy

WHO's post-2015 End TB Strategy, adopted by the World Health Assembly in 2014, aims to end the global TB epidemic as part of the newly adopted Sustainable Development Goals (SDG). It serves as a blueprint for countries to reduce TB incidence by 80%, and TB deaths by 90%, and to eliminate catastrophic costs for TB-affected households by 2030 The End TB strategy encompasses a package of interventions that can be fully adapted at the country level. The strategy provides a unified response to ending TB deaths, disease, and suffering and builds on three strategic pillars underpinned by four key principles. The three pillars bring together critical interventions to ensure that all people with TB have equitable access to high-quality diagnosis, treatment, care, and prevention, without facing catastrophic expenditure or social repercussions.

Figure 1: ***END TB Strategy-Pillars and underlying principles***

Pillar one of the End TB strategies puts patients at the heart of service delivery through integrated, patient-centered care and prevention. The four key components of pillar one are (i) Early diagnosis of TB including universal drug susceptibility testing (DST), and systematic screening of contacts and high-risk groups. (ii) Treatment of all people with TB including drug-resistant TB, and patient support. (iii) Collaborative TB/HIV activities and management of comorbidities (iv) Preventive treatment of persons at high risk and vaccination against TB.

Table 2*: End TB strategy Vision, goal milestones, and Targets*

VISION	A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis
GOAL	End the global tuberculosis epidemic
MILESTONES FOR 2025	75% reduction in tuberculosis deaths (compared with 2015) 50% reduction in tuberculosis incidence rate (less than 55 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis
TARGETS FOR 2035	95% reduction in tuberculosis deaths (compared with 2015) 90% reduction in tuberculosis incidence rate (less than 10 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis
PRINCIPLES 1. Government stewardship and accountability, with monitoring and evaluation 2. Strong coalition with civil society organizations and communities 3. Protection and promotion of human rights, ethics and equity 4. Adaptation of the strategy and targets at country level, with global collaboration	
PILLARS AND COMPONENTS	
1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support C. Collaborative tuberculosis/HIV activities, and management of comorbidities D. Preventive treatment of persons at high risk, and vaccination against tuberculosis	
2. BOLD POLICIES AND SUPPORTIVE SYSTEMS A. Political commitment with adequate resources for tuberculosis care and prevention B. Engagement of communities, civil society organizations, and public and private care providers C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control D. Social protection, poverty alleviation and actions on other determinants of tuberculosis	
3. INTENSIFIED RESEARCH AND INNOVATION A. Discovery, development and rapid uptake of new tools, interventions and strategies B. Research to optimize implementation and impact, and promote innovations	

Regarding TB diagnosis and detection of drug resistance, the End TB strategy calls for WHO-endorsed rapid diagnostic tools (WRD) for early diagnosis and prompt TB treatment, rapid DST for at least R for all bacteriologically confirmed TB patients, and DST for FQ for all RR-TB patients.

Table 3: *End TB strategy milestone and targets*

VISION	A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis			
GOAL	End the global tuberculosis epidemic			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

Recently, the **second United Nations General Assembly high-level meeting on the fight against TB was held on 22 September 2023** and brought together Heads of State and other leaders to revitalize commitments and actions to accelerate efforts to end TB. Universal access to TB prevention and care as part of the universal health coverage (UHC) agenda, multisectoral actions to address drivers and determinants of the TB epidemic as part of the sustainable development agenda, strengthening essential TB services as part of the pandemic preparedness, prevention and response agenda and advancing research and innovation are the key priorities to drive the End TB agenda forward[3]. WHO Director General's Flagship Initiative on TB sets targets for the next 5 years that informed the political declaration of the second UN High-Level Meeting on TB.

1.3.3. Global Progress and challenges in TB control/end TB

Globally, the annual number of people diagnosed with TB and to have accessed TB treatment has steadily grown from about **6 million in 2015 to 7.5 million in 2022**, but still, as many as **30% of the estimated cases were missed** out on diagnosis and care. TB incidence and deaths are falling, but not fast enough to reach the first milestone of the End TB strategy. The Covid pandemic halted the progress in TB control with a decline in notifications.

Laboratory methods for the diagnosis of TB are continually evolving to achieve more rapid, accurate, and cost-effective results. In parallel with the scale-up of more sensitive diagnostic tools, an increase in the proportion of bacteriologically confirmed PTB was reported from 57% in 2015 to 63% in 2022.

Globally, testing of bacteriologically confirmed TB cases for R resistance, has increased from 7% in 2012 to 73% in 2022 (73% for new and 79% for previously treated TB patients). In parallel, MDR/RR-TB cases diagnosed and initiated on treatment increased from 122K in 2015 to 175K in 2022.

Testing coverage for resistance to Fluoroquinolone (FQ) forms a critical component of recommended treatment regimens for both R-resistant and R-sensitive TB. Diagnostic algorithms for drug resistance detection are often driven by testing for resistance to R, with further DST only for RR-TB patients. As a result, isoniazid (H) resistance among R-sensitive populations remains mostly

[3] https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/featured-topics/un-declaration-on-tb#:~:text=On%2022%20September%202023%2C%20at,time%2Dbound%20targets%20and%20actions.

undetected, and often not treated with the WHO-recommended modified regimen, thus risking poorer treatment outcomes and the development of further resistance.

1.4. TB Epidemiology and TB Control in Pakistan

1.4.1. Country Overview

The Islamic Republic of Pakistan is a country in South Asia spanning over 881,913 square kilometers (340,509 square miles) with a 1,046-kilometer (650-mile) coastline along the Arabian Sea and the Gulf of Oman in the south. The country is bordered by India to the east, Afghanistan to the west, Iran to the southwest, and China in the far northeast.

The country is administratively divided into four provinces namely, Punjab, Sindh. Khyber Pakhtunkhwa (KP) and Baluchistan, two regions including Azad Jammu Kashmir (AJK) and Gilgit Baltistan (GB), and Islamabad Capital Territory (ICT).

Pakistan is the world's fifth-most populous country, with an estimated population of 247 million (2023). In 2023, the Pakistan Bureau of Statistics conducted the 7th Population and Housing Census. Punjab and Sindh are the country's most densely populated provinces. The average population density is 287/sq. km. which varies greatly between provinces and districts. Sixty-six percent of the population lives in rural areas and 40% of the urban population lives in slums.

Table 4*: Population of various regions of Pakistan (2023)*

Province / Region	Capital	Population	(%)
Punjab	Lahore	125,214,937	(51%)
Sindh	Karachi	55424331	(22%)
Khyber Pakhtunkhwa (+FATA)	Peshawar	41,946,377	(17%)
Baluchistan	Quetta	15,454,966	(6%)
Gilgit-Baltistan	Gilgit	1727700	(1%)
Azad Jammu & Kashmir	Muzaffarabad	4494823	(2%)
Islamabad Capital Territory	Islamabad	2675199	(1%)

Pakistan is a lower middle-income country with nominal GDP per capita of $1,516 and an estimated 4% of the population is living below the international poverty line. Total life expectancy at birth is 66.4 years and approximately 35% of the population is under 15 years of age. The prevalence of undernourishment is 12% and 0.1% of the population is infected with HIV, 12% of females and 13% of males have diabetes, whereas smoking is prevalent in 3% of females and 38% of males. The HIV epidemic is concentrated in key populations including people who inject drugs. Factors like poverty, malnutrition, poor housing and sanitation, inadequate health care facilities, population migration and urbanization, political instability, and refugees are key challenges in health care in the country.

1.4.2. Health care System

Pakistan's health care system includes public health departments, government and non-government organizations, and private entities providing for-profit and not-for-profit health care services. Two-thirds of the population initially access health care through the private sector, which is largely unregulated. The Federal Ministry of Health was dissolved in 2011, and responsibility for

health services was devolved to the provinces. Provincial health care commissions are working to develop and enforce Minimum Service Delivery Standards. The public sector provides preventive and hospital care to the urban and rural population. Communicable diseases are still the leading causes of morbidity and mortality, while non-communicable diseases are on the rise.

1.4.3. TB burden in Pakistan

Pakistan ranks 5th among 30 high-burden countries for TB with an estimated incidence of 686,000, at the rate of 277 per 100,000 people (2023). Estimated TB cases in Pakistan are attributed to five risk factors including undernourishment (165k), smoking (38k), diabetes (31K), HIV (14k), and alcohol (4.9K) in 2022.

Drug-resistant TB: Pakistan is also among the top five high drug-resistant TB burdens countries with an estimated incidence of 15000 MDR/RR-TB.

Table 5*: Estimated TB incidence by age and sex 2023*

	0-14 years	> 14 years	Total
Females	32765	251200	283,965
Males	36406	316730	353,136
Total	**69,171**	**567,930**	**637,101**

1.4.4. Progress and challenges in TB control effort.

In Pakistan, *the implementation* of the DOTS strategy started in 2001. TB care services were established and integrated within the public health sector in the initial five years. In the next five years, the TB program focused on improving the quality of diagnostic services and expansion of DOTS coverage in the private sector. Starting in 2009, services were expanded to include programmatic management of drug-resistant TB, scale-up of rapid molecular diagnosis, culture and DST services, private sector engagement, childhood TB and active case findings. Starting in 2021, preventive TB treatment was included in key strategies to end TB.

1.4.5. TB care and diagnostic services

The TB diagnosis relied totally on AFB microscopy for the initial 15 years of DOTS implementation. Xpert was introduced in 2011, very soon after its endorsement by WHO. However, its expansion and uptake were gradual, and the diagnostic algorithm was modified over time in parallel with improved coverage. Xpert was initially recommended for people at risk of DR-TB and those with immunocompromised conditions. In 2015, recommendations were expanded to cover the diagnosis of TB in children and EPTB, and in 2017 for R testing of all bacteriologically confirmed TB patients and for diagnosis of people with abnormal chest X-rays. Since 2021, Xpert testing is recommended for all patients with signs and symptoms of TB. In 2023, about 1300 TB management units (TBMU) and 1,949 laboratories, including 809 in the private sector, offered TB diagnosis. Xpert testing facilities were made available in 453 of the laboratories by 2023.

Table 6: ***TB care and diagnostic services in Pakistan (2023)***

TB Care services	BMUs	GP Clinics	PMDT	TB-HIV
	1,300	**13,000**	**63**	**55**
Public	1,140	-	59	55
Private	160	13,000	4	-
TB Diagnostic facilities	**Microscopy**	**Xpert**	**Culture**	**DST**
	1,949	**453**	**19**	**7**
Public	1,140	413	18	5
Private	809	40	1	2

Engagement of private sector in TB care: There is a large private sector in Pakistan. Most of the population has their first contact with a private health care provider; therefore, interventions to engage private practitioners in TB care services were prioritized. Many private facilities, including solo private practitioners, private hospitals/ clinics, NGOs, pharmacies, and informal practitioners, are involved in managing TB. Public-Private Mix (PPM) aims to establish linkages between private practitioners and the public sector to improve access and standardize TB care.

1.4.6. TB surveillance system

Each TBMU maintains a standard TB register, in which individual patient data (IPD) is recorded for all notified TB patients. At the end of each quarter, all reporting TBMUs prepare a TB notification report in a standard format. The facility report is consolidated into a district report and further into provincial reports. Provincial TB programs validate and submit these reports to the surveillance unit of the National Tuberculosis Program (NTP). Treatment outcome data is reported after one year.

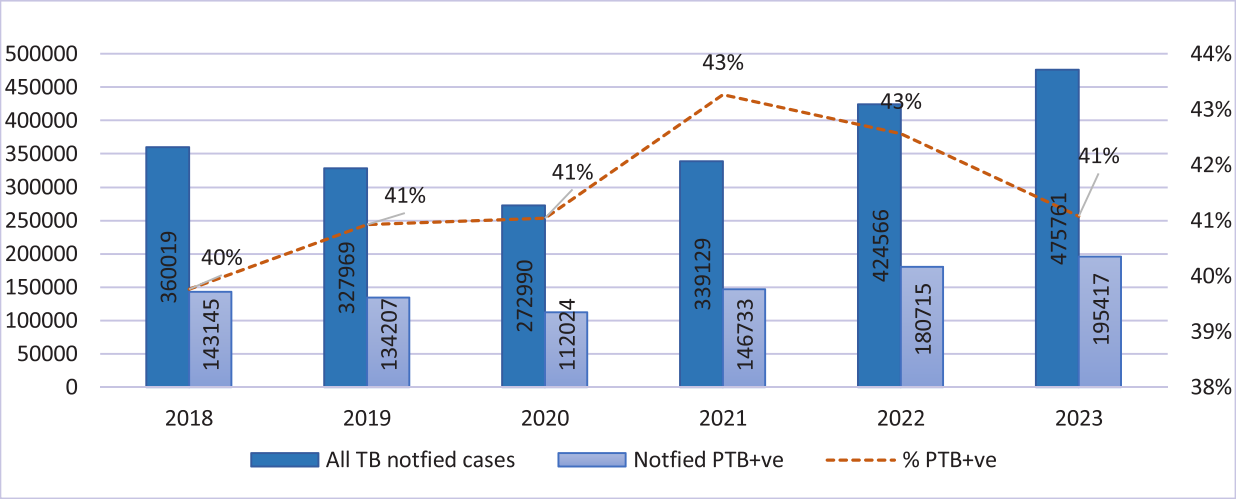
In 2018, the DHIS2 aggregate module was implemented, and the facility notification report was entered digitally. In Q-4, 2023, electronic case-based data entry started on the DHIS2 tracker.

For RRTB notification, the PMDT treatment site generates separate quarterly reports for notified RR-TB patients initiated on second-line TB treatment. Treatment outcome reports are generated after two years.

1.4.7. TB Notification, treatment coverage, and Outcomes

A gradual increase in TB notification was seen between 2001-2015. TB notifications remained stagnant during 2016-18 followed by a decline in 2019. A sharp decline in TB notification was seen in 2020 due to COVID-19 pandemic, with partial recovery in 2021 whereas TB notification in 2022 superseded compared to any previous years. However, despite the increase in notification and improved coverage of mWRD proportion of Bacteriological confirmed PTB is constant around 41% of the notified TB cases.

Figure 2: TB Notific*ation and proportion of Bacteriological confirmed PTB*



Case contribution by the private sector: Parallel with the enhanced engagement of the private health sector in TB control, the private sector's contribution to TB notification gradually increased from 27% in 2016 to 46% in 2023.

Although a significant decline is seen in TB mortality from 56 to 20/100k population but a very slow decline is noted in TB incidence over the years, and with the current pace, it may take decades to control TB in the country.

Table 7*: National TB case notification pattern by disease site and previous TB treatment 2023*

	Incident TB cases notification					Previously treated TB cases				
	New	Relapse	Un known	Total		TX after Failure	Tx after loss to Follow-	Other	Total	
PTB-Bacterilogically confirmed	184,598	10,499	320	195,417	41%	861	901	867	2629	60%
PTB-Clinically diagnosed	188,309	3,454	227	191,990	40%	35	482	653	1170	27%
EPTB	87,362	901	91	88,354	19%	115	125	336	576	13%
	460,269	**14,854**	**638**	**475,761**	100%	**1,011**	**1,508**	**1,856**	**4,375**	100%

Among the notified cases, 14% are pediatric cases. 47% of the patients are from the economically productive age group (15-44 years). 12% are aged 65 and above, while 48% are females. The details of age and gender-wise break up is as below:

Table 8: ***Estimated TB incidence and TB notification by public and private sector***

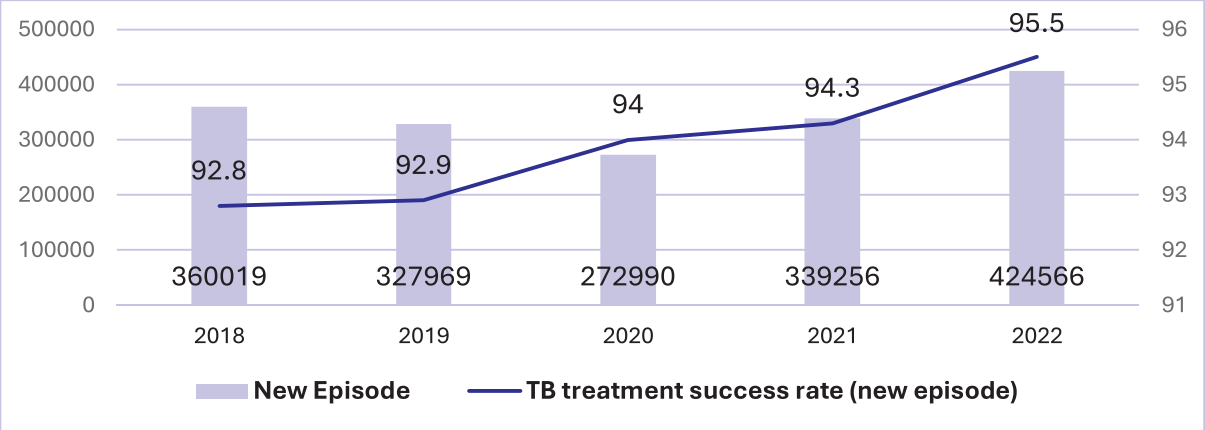
Province/ Region	Estimated Incident TB cases	Incident TB case notification				CNR	CDR
		Total	Public sector	Private sector			
Punjab	323,055	275,752	161,301	114,451	**44%**	220	85%
Sindh	142,995	111,633	51,986	59,647	**53%**	201	78%
KP+NMD	108,222	59,098	31,241	27,857	**47%**	141	55%
Baluchistan	39,874	15,090	10,450	4,640	**31%**	98	38%
AJ&K	11,597	6,465	4,682	1783	**28%**	144	56%
GB	4,457	4,347	3,554	793	**18%**	252	98%
ICT	6,902	3,376	1,385	1991	**59%**	126	49%
TOTAL	**637,101**	**475,761**	**264,599**	**211,162**	**46%**	**193**	**75%**

NMD: newly merged districts

The proportion of **bacteriologically confirmed PTB cases being tested for R resistance** is gradually improving along with the enhanced coverage of Xpert testing. In 2022, 72% of new and 84% of previously treated PTB cases were tested for R-resistance.

Treatment Outcomes: Since 2013, treatment success rate (TSR) for drug-sensitive TB is maintained at above 90%.

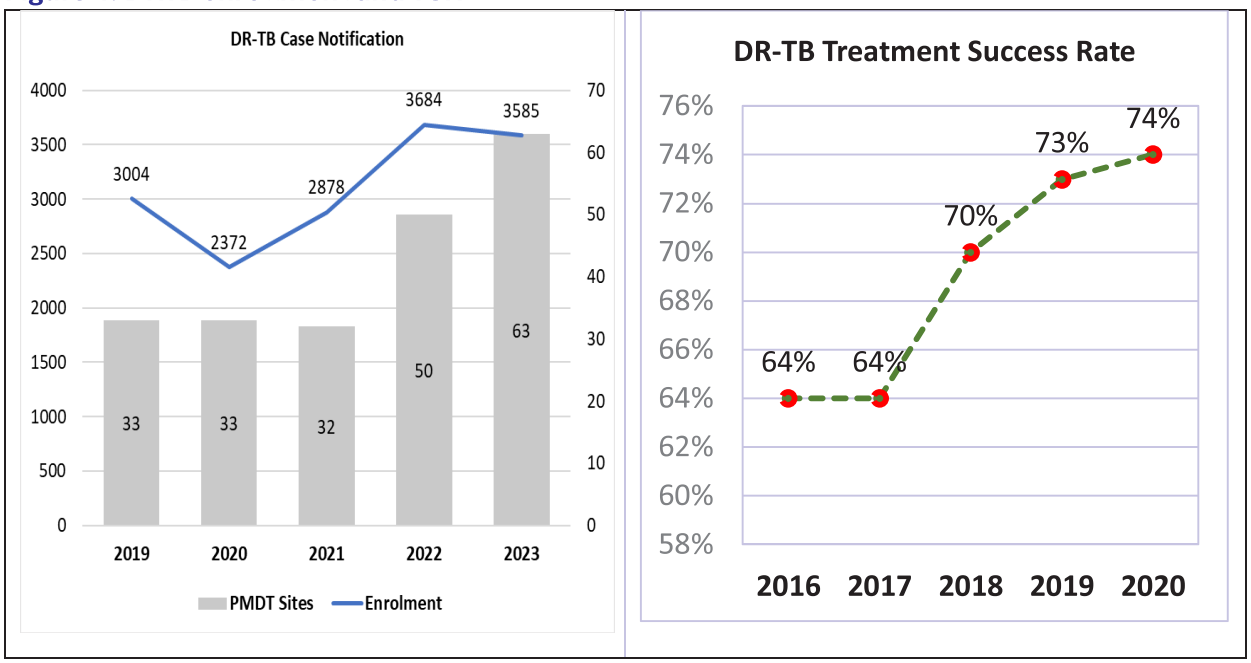
Figure 3: ***Five-year trend of treatment success rate***



1.4.8. RRTB/MDR-TB Enrolment and Treatment Success Rate

Simultaneous to scale up mWRD a gradual increase was seen in MDR/RR-TB patients diagnosed and initiated on second-line treatment from 200 in 2009 to approximately 3500 annually. Among MDR/RR-TB patients, almost 40% are pre-Extensively Drug Resistance (XDR) TB.

Figure 4: DRTB *enrollment and TSR*



With the introduction of Bedaquiline and other new drugs containing shorter treatment regimens for MDR/RR-TB patients, an improvement in TSR is noted from 64% in 2015-2017 to 73% in 2018-19 alongside reports of acquired resistance to Bedaquiline.

Missing TB cases

The National TB Control Program notified 475,761 TB cases in 2023, against the estimated TB incidence of 637,101 cases. Thus, around 161,340 around 26% of estimated TB cases were either not notified or diagnosed in 2023. Based on estimates, there are many missed cases in the age group 65 and above due to higher prevalence (1,100 / 100K).

Table 9: *Missing TB cases by Provinces 2023*

	Punjab	Sindh	KP+ NMD	Balochistan	AJ&K	GB	ICT	TOTAL
Incident TB cases	275,752	111,633	59,098	15,090	6,465	4,347	3,376	**475,761**
Missed TB Cases	47,303	31,362	49,124	24,784	5,132	110	3,526	**161,340**
Missed %	**15%**	**22%**	**45%**	**62%**	**44%**	**2%**	**51%**	**25%**

Gaps between the estimated incidence and notification are due to a mixture of underreporting of detected cases and underdiagnoses (either because people do not access health care or because they are not diagnosed).

1.5. Mandatory TB case notification

TB has been declared as a notifiable disease in Pakistan through an act of parliament which speaks: "All registered medical practitioners shall submit a complete Notification Form as provided in notification to district health authorities within a week"

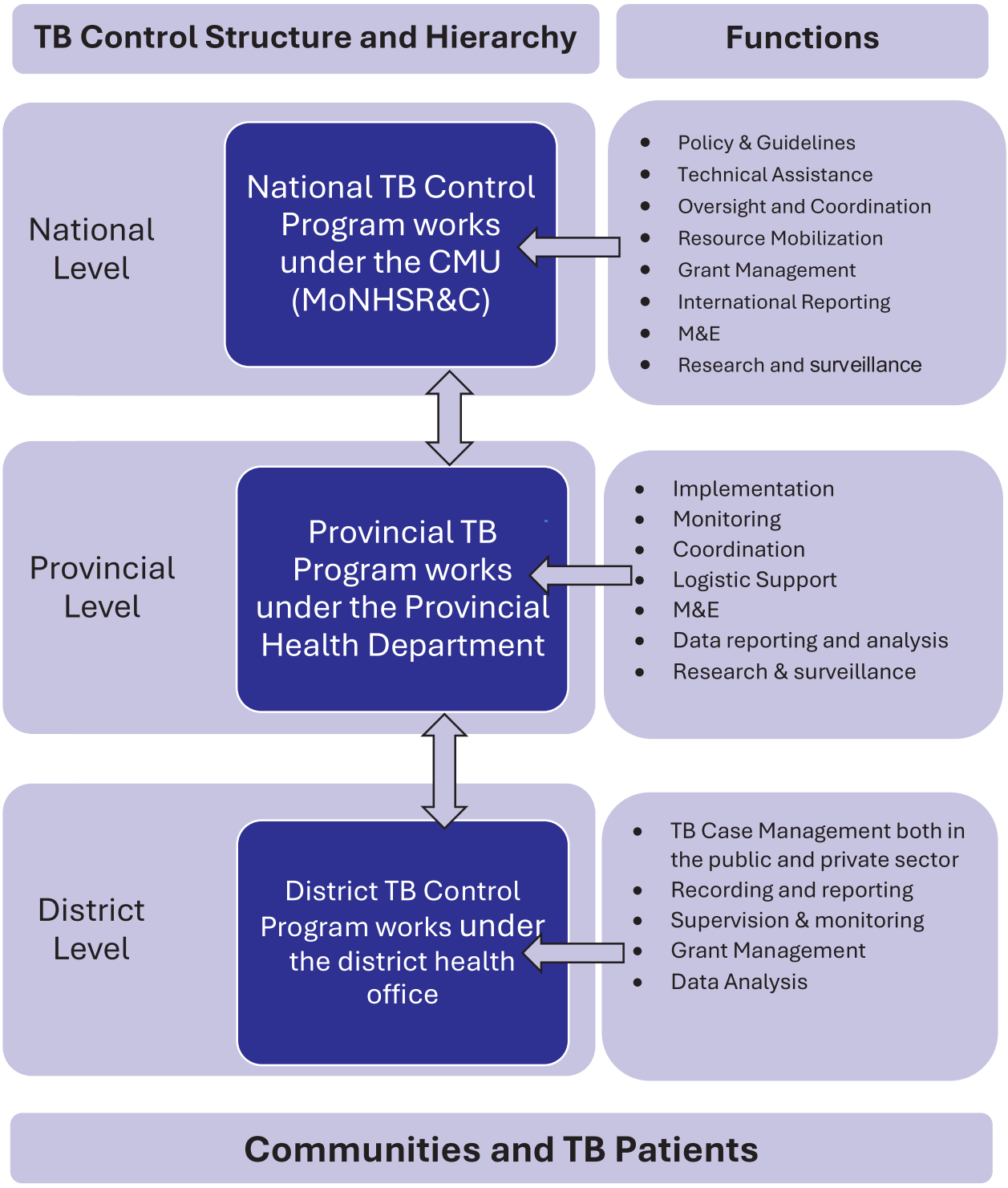
Notification of TB cases through effective implementation of this act can greatly increase notification. This has been witnessed in several initiatives taken by National TB Program from time to time

- In 2016 SAIPs pilot project supported by USAID engaged 500 pharmacies in 5 major cities of Pakistan and great potential to enhance TB notification by engaging pharmacies was concluded.
- in 2016 through Global fund Grant, 2000 pharmacies were engaged and intervention contributed 2200 TB patients.
- In 2017, the community pharmacy–referral network achieved an annual referral rate of 3,025 presumptive TB patients and diagnosis of 547 active TB cases.
- In 2019, NTP through Global fund support pilots tested implementation of MCN in 5 districts and private health care providers (not formally engaged through PPM) were enabled to notify the TB case. An increase of 11% of TB notification was noted in intervention district in one year.
- In 2021, pilot project supported by TB Reach engaged 3000 pharmacies in 4 districts in Punjab and reported 15,000 TB patients in the year 2021.

1.6. TB Control Structure and Functions

The TB Control Program operates with a hierarchical structure. The federal level is responsible for policymaking, technical assistance, and research. The provincial level is the primary implementation entity, while the district level is responsible for detecting and managing TB cases throughout treatment.

Figure 5*: TB Control Program-Hierarchy and Functions*



1.7. NTP Pakistan's Response– National Strategic Plan 2024-2026

Pakistan adopted SDGs 2030 agenda through a unanimous resolution of parliament. The seven pillars of Vision-2025 are fully aligned with the SDGs, providing a comprehensive long-term strategy for achieving inclusive growth and sustainable development.

The ***National TB strategic plan (2023-2026)*** aims to reduce the TB mortality rate by 35% in 2026 compared to 2015. It aligns with the WHO End TB strategy and proposes bold strategies to end TB in the country in line with SDGs, End TB strategy, and the accelerated efforts to end TB. This NSP covers the years 2023 to 2026; it describes the operationalization of the strategic interventions and activities that need to be developed or implemented. It specifies the indicators to be used for monitoring and evaluation and identifies the technical assistance needs.

GOAL AND OBJECTIVES

Goal: To reduce the TB mortality rate by 35% in 2026 compared to 2015.

Objective 1: To increase the number of notified new TB episodes to at least 493,520 by 2026 and to maintain TB treatment success rate at more than 90% from 2024 onwards.

Objective 2: To increase the number of detected and treated of MDR/RR-TB cases from 3,373 in 2021 to at least 7,700 by 2026 and their treatment success rate to at least 80% from 2024 onwards.

Objective 3: To increase the proportion of notified TB cases with known HIV status from 52% in 2021 to at least 95% by 2026 and to treat 100% of identified TB/HIV with ART every year.

Objective 4: To improve and enhance TB prevention through i) tuberculosis preventive therapy of, at least 80% of household contacts and PLHIV with no active TB in 2023 to 2026 and ii) strengthening infection control.

Objective 5: To improve and strengthen the governance and the programmatic management capacities for providing TB services at national, provincial and district levels.

Objective 6: To preserve the key TB prevention, care and control services in the areas in the acute phase of a complex emergency.

Chapter 2

TB Case Finding and TB Screening

1. 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.

2.1 Passive TB case finding

This is a patient-initiated pathway to TB diagnosis and 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.***

2.1.1. Identification of presumptive TB

A presumptive TB is typically identified on following symptoms

2.1.1.1. Signs and symptoms

- Cough >2 weeks
- Cough of any duration with one or more associated TB symptoms*
    - Expectoration
    - Fever*
    - Night Sweats*
    - Weight loss*
    - Loss of appetite
    - Fatigue
    - Weakness
    - 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.

2.1.1.2. Chest X-ray

- Patient with abnormal shadows on chest X-ray consistent with TB. Chest X-ray is recommended as initial screening subject to availability.

2.1.2. Laboratory diagnosis of TB

For all presumptive TB, laboratory testing using WHO-recommended rapid diagnostic test should be used for bacteriological diagnosis of TB. (see chapter on TB diagnosis).

2.1.3. How to enhance patient-initiated pathway to TB diagnosis

TB diagnosis by passive case finding shall remain primary approach for case finding and should be enhanced by following approaches:

2.1.3.1 Improve access to care:

- *Improve access to testing and diagnosis* by extending and improving capacity of diagnostic and testing services of mWRDs (Xpert MTB/RIF), scaling up sputum collection and transport systems and improving the system of reporting results from the laboratory to the clinician.

This will also require ensuring sufficient laboratory requirements, including human resources, and improving links between the private and public sectors.

- Providing access to CXR services and CAD: Greater use of CXR and other accurate tools for diagnosing TB
- *Improving the diagnosis of bacteriologically negative TB, extrapulmonary TB and TB in children*
- *Strengthening primary health care services*
- *Improving referrals and notifications by all care providers.*
- *Establish and strengthen a functional specimen transport system*
- *Reducing the direct and indirect costs to patients associated with seeking care*
- *Providing social protection schemes where possible and necessary.*

2.1.3.1. Improving the acceptability of care:

*E*nsuring privacy and providing fast-tracking through outpatient departments and faster services to reduce waiting times. Mechanisms should be put in place to ensure that daily wage-earners maintain income.

Incorporating "care" aspects, by including emotional care in addition to diagnosis and treatment in training curricula to ensure empathetic, compassionate and patient-centered care.

2.1.3.2. Training and capacity-building of health-care workers:

By providing additional training and equipping all health-care workers in the health system, in both the public and the private sectors, in primary care, at entry points to health care and lay community workers and volunteers *to* increase the likelihood that individuals with symptoms of TB who seek care are recognized and referred for appropriate evaluation and care.

2.1.3.3. Community engagement and demand generation:

Education and awareness campaigns (including on exposure and risk) for the general public and in communities that are at higher risk of TB to increase the likelihood that those who have been exposed and/or have TB disease will seek care at facilities with the capacity to diagnose and treat TB.

2.2. Active case finding

Detecting TB only among people who present to health facilities by passive case-finding approaches is not enough to find all people with TB disease. The remaining case-detection gap, 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.

Active Case finding is a provider-initiated TB screening pathway which systematically targets people at high risk of exposure or of developing TB disease. This approach can target people at different stages of TB, for example, by screening those:

- Who are at high risk of exposure (e.g. high TB burden communities or settings such as prisons) or
- who are exposed to TB (e.g. contacts of a TB patient), or
- who have high risk of developing TB (e.g. people living with HIV).

Objective of Active case findings

The two primary objectives of Active case finding are to augment standard TB care practices at individual and the community level. For individuals with TB disease, the **first objective** is to ensure that TB disease is detected early and treatment is initiated promptly by bypassing many of the barriers to diagnosis and care for people suffering from TB disease with the ultimate aim of reducing the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB; the **second objective** is to reduce the community-level prevalence of TB disease, thus reducing transmission of *Mycobacterium tuberculosis* and averting future incident TB.
Thus, TB screening can play a critical role in

- *Addressing the case detection gap*: By finding missing TB cases by reaching out to people who are not reached by the patient- initiated pathway.
- *Reaching the most vulnerable groups*: Those with the highest risk for TB with limited access to health care.
- *Enabling initiation of TB preventive treatment*: by identifying eligible population during process of Systematic screening for TB disease.

2.2.1. Systematic Screening for TB (Whom to screen)

Systematic screening is defined as "The systematic identification of people at risk for TB disease, in a pre-determined target group, by assessing symptoms and using tests, examinations, or other rapidly applied procedures." The WHO End TB Strategy includes systematic screening for TB disease in high-risk groups as a central component of its first pillar.
It is recommended for **people who do not seek health care** because i) they do not have or recognize symptoms, ii) they do not perceive that they have a health problem that warrants medical attention, iii) there are barriers to accessing care, or for other reasons. It may also target **people seeking health care** who do or do not have symptoms or signs compatible with TB and who may not be identified by passive case-finding as possibly having TB. People seeking care who may be eligible for TB screening include, i) people with medical conditions that constitute risk factors for TB (such as people living with HIV or diabetes mellitus) ii) who may be seeking care for reasons other than symptoms compatible with TB.

WHO has issued guidance on screening of seven different target population shown in summary table 10. Based on evidence, screening is strongly recommended of People living with HIV, household and other close contacts of individuals with TB disease, Prisons and penitentiary institutions and Miners and others exposed to silica dust. Whereas conditional recommendation is issued for other three target population group including general population (prevalence >0.5%), People with structural risk factors of TB and people attending health care services who have clinical risk factors for TB (Table 10).

Recommended Risk group for Systematic screening for TB in Pakistan

High risk groups: It is strongly recommended that the following high-risk groups should always be systematically screened for TB

a. Household and close contacts (including children) of people with bacteriologically confirmed TB
b. People living with HIV (including children)
c. Prisoners
d. Miners exposed to silica dust (Glass factory)

Table 10*: WHO-recommended Target population for systematic screening*

	Target Population	WHO Recommendation	
1	General Population	Systematic screening for TB disease may be conducted among the general population in areas with an estimated TB prevalence of 0.5% or higher	Conditional recommendation, low certainty of evidence
2	People with structural risk factors of TB	Systematic screening for TB disease among people with structural risk factors for TB. These include **urban poor** communities, **homeless communities**, communities in remote or isolated areas, **indigenous populations, migrants, refugees, internally displaced persons** and other vulnerable or marginalized groups with limited access to health care	Conditional recommendation, very low certainty of evidence
3	People living with HIV	People living with HIV should be systematically screened for TB disease at each visit to a health facility	Strong recommendation, very low certainty of evidence).
4	Household and other close contacts of individuals with TB disease	Household contacts and other close contacts of individuals with TB disease should be systematically screened for TB disease	Strong recommendation, moderate certainty of evidence
5	People in Prisons and penitentiary institutions	Systematic screening for TB disease should be conducted in prisons and penitentiary institutions	Strong recommendation, very low certainty of evidence
6	Miners and others exposed to silica dust	Current and former workers in workplaces with silica exposure should be systematically screened for TB disease	Strong recommendation, low certainty of evidence).
7	People attending health care services who have clinical risk factors for TB	In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor for TB who are either seeking health care or who are already in care	Conditional recommendation, very low certainty of evidence).
		People with an untreated fibrotic lesion seen on chest X-ray may be systematically screened for TB disease	conditional recommendation, very low certainty of evidence

For these four risk groups, the focus should be on *how* to screen and on the quality of screening. The assessment should include the size and distribution of the group, the TB burden in the group, past and current screening experience and any remaining considerations and challenges to be addressed to optimize screening

Other risk groups: It is recommended that TB screening for all other risk groups be prioritized based on evidence. Any planning for scale-up should be based on the availability of resources and the results of initial implementation experience, cost-effectiveness, and cost-benefit analysis. Furthermore, plans for screening new risk groups should first be pilot-tested and evaluated.
A list of other higher-risk groups and potential recommended sites for screening is given in Table 11.

2.2.2. 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 and should be ideally implemented where high-quality TB diagnostic and treatment services are available.

Principle 2: Screening should reach the people at greatest risk of developing TB disease, including high-risk groups and communities with a high prevalence of TB.

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, feasibility and cost. A highly sensitive tool (X-ray) for screening to identify people with presumptive TB and a sensitive test (WRD) to confirm TB diagnosis should be used

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

Principle 6: Screening program should be regularly monitored to inform any re-prioritization of risk groups, resource use, adaptation of screening approaches and discontinuation of screening.

Table 11: *TB risk groups and potential site of screening*

Potential site of screening	Risk group	
Outpatient and hospital inpatient departments and primary health-care centers	People attending health care services who have clinical risk factors for TB	People previously treated for or exposed to TB
		People with an untreated fibrotic lesion shown on CXR
		People with chronic respiratory disease
		People presenting with pneumonia
		People with diabetes mellitus
		People who smoke
		Undernourished people or people with a body mass index ≤ 18
		People who have had a gastrectomy or Jejuno-ileal bypass
		People with alcohol use disorder or drug use disorder
		People with chronic renal failure
		People on treatments that compromise their immune system
		Older people (60 years and older)
		Women who are pregnant (and up to 3 months postpartum)
		General outpatients and inpatients (in settings where the prevalence of both TB and of TB risk factors is high, it may be logistically more feasible to screen all health center attendees)
		People in mental health clinics or institutions
Community	General population	Populations of geographical areas with a high prevalence of TB (estimated to be 0.5% or higher)
Community	Subpopulations with limited access to health care and with structural risk factors for TB	Subpopulations with limited access to health care and with structural risk factors for TB, including those living in poor urban communities, homeless communities, communities in remote or isolated areas, indigenous or tribal communities or other vulnerable or marginalized groups with limited access to health care
Residential institutions	Subpopulations with limited access to health care and with structural risk factors for TB	People living in shelters
		Other congregate institutions (such as the military)
		Immigrants from settings with a high prevalence of TB
Immigration and refugee services	Subpopulations with limited access to health care and with structural risk factors for TB	People in refugee camps
		Internally displaced persons
		Migrant workers
Workplaces with high occupational exposure		People working in TB or veterinary medicine laboratories
		Prison guards and other workers in penitentiary facilities
		Other workplaces with a high prevalence of TB
		Health-care worker

2.2.3. 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 need to be followed by a diagnostic test, offered as a part of a comprehensive clinical evaluation, to confirm or rule out TB disease in individuals who are screened for TB.

Screening tests should distinguish between people with a high likelihood of having TB disease from those who are unlikely to have TB. A screening test is not intended to be diagnostic, people screen positive, should be referred for diagnostic evaluation with bacteriological testing to confirm or rule out TB disease. The tools for initial screening of the general population and high-risk groups (not including people living with HIV) should include symptom screening for clinical features associated with pulmonary TB (including cough, hemoptysis, weight loss, fever or night sweats) and screening with CXR.

2.2.3.1. Symptom Screening:

Symptom screening is feasible, easy to implement and low-cost. It is also highly acceptable because it is non-invasive 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 the disease. Symptom screening has, however, low and variable sensitivity, especially for detecting TB early. The positivity rate for screening with symptoms differs from setting to setting, depending on the prevalence of other, non-TB conditions and the screening quality. In particular, the occurrence of cough may vary with the frequency of other lung conditions, smoking and levels of air pollution.

Cough: The review performed by WHO for the 2021 guidelines update estimates the sensitivity of screening for *any* cough for detection of TB disease is 51%, which implies that, in many settings, about half of people with TB do not cough; therefore, screening for this clinical feature alone would detect only about half of people with TB disease. Screening for prolonged cough – defined as lasting ≥ 2 weeks – is estimated to be even less sensitive (42%) but highly specific (94%).

For systematic screening of high-risk groups, it is recommended that “cough of any duration” should be used for screening when CXR facility is not available and “cough of longer duration” shall be used when combined symptoms and CXR is used for screening. (Figure-3)

2.2.3.2. CXR Screening

CXR is a rapid imaging technique for identifying lung abnormalities. It is used in clinical evaluation for conditions of the thoracic cavity. 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. The sensitivity of CXR for the threshold of "any abnormality" is estimated to be 94%, and its specificity is estimated to be 89%. For a threshold of an "abnormality suggestive of TB", the estimated sensitivity is lower (85%) but the specificity is higher (96%).

The low specificity of CXR means that a significant proportion of individuals without TB will have an abnormal test result. However, using CXR screening can help identify patients with a higher likelihood of having TB and thus reduce the cost of conducting a large number of tests to detect a confirmed TB case. From the perspective of the person being screened, CXR is valuable because it can also detect medical conditions other than TB, including other pulmonary and thoracic conditions.

Thus, either "any abnormality" or "abnormality suggestive of TB" detected by CXR should be used, depending on the context, radiological expertise, the availability of other resources, including diagnostic testing, and a preference for higher sensitivity or for higher specificity of the screening algorithm.

CXR is used for screening in pre-identified groups in a community or special setting to find active TB cases. Mobile vans with X-rays, with or without Xpert, are being used in the outreach camps conducted in selected districts of Pakistan to find active cases. Screening tools used to screen different populations and age groups are described in the table below:

2.2.3.3. Computer aided diagnosis (CAD) technologies for CXR screening

CAD software packages have been introduced to automate interpretation of digital CXR images for pulmonary TB disease-related abnormalities.

> CAD products analyze digital CXR images and generate a continuous numerical score that corresponds to an increasing likelihood of TB as the score increases. The scores are usually between 0 and 1 or 1 and 100 but are not percentages. An abnormality score ranging from 0 to 100, with higher scores indicating a greater likelihood of TB (>70). A threshold score is the score below which TB is ruled out.

CAD can resolve numerous difficulties in human interpretation of CXR. These include the lack or scarcity of trained health personnel to interpret radiographic images for TB screening and substantial intra- and inter-reader variation in correct detection of abnormalities associated with TB. CAD could thus allow significant scale-up of TB screening and increase access to CXR screening. The score given by CAD when reading a chest film relates solely to the likelihood of TB; in contrast a human reader can identify between multiple pathologies simultaneously when interpreting a CXR

The use of CAD software program is recommended to be used in place of human readers for interpretation of digital CXR in screening and triage for TB disease. The current recommendations are specific to adults and adolescents aged 15 years and older and applies only to interpretation of antero-posterior or posteroanterior views of digital plain CXR for pulmonary TB.

If a program includes using CAD for automated interpretation of CXRs as part of screening or triage, calibration is essential to determine the appropriate threshold score for any given setting and program according to the spectrum of radiographic findings in members of the target population with and without TB disease.

2.2.4. Recommended Algorithms for screening in Pakistan

WHO evaluated the performance of different screening algorithms in different populations, and the results are shown in Table 12. The prevalence of TB and risks of poor health outcomes or mortality, logistical factors associated with the likely location of screening, and considerations for initiating TPT for certain risk groups all influence the choice of screening algorithm.

Table 12: ***Diagnostic yield of different screening algorithms in different populations***

Populations	Option	Recommended screening algorithms	Recommended Diagnostic test	Estimated prevalent cases detected
General population and high-risk groups (not including people living with HIV)	1	Parallel screening with any TB symptom and CXR*	mWRD	85%
	2	Screening with any TB symptom	mWRD	60%
Adults and adolescents living with HIV	1	Parallel screening algorithm with W4SS and CXR*	mWRD	71%
	2	W4SS single screening algorithm	mWRD	63%
Child contact <15yrs	1	Parallel screening with symptoms and CXR	mWRD	
	2	Screening with symptoms	mWRD	
children <10 years living with HIV	1	Screening with symptoms	mWRD	

2.2.5. 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. If clinical suspicion of TB is still high, a negative diagnostic test result may be followed up by further clinical evaluation. This could include re-testing with the same or another diagnostic method and/or close follow-up of clinical symptoms with or without chest imaging. If the positive predictive value of the test result is low, a positive diagnostic test result might have to be re-confirmed with further testing and clinical evaluation.

2.2.6 Considerations for systemic screening for high-risk groups

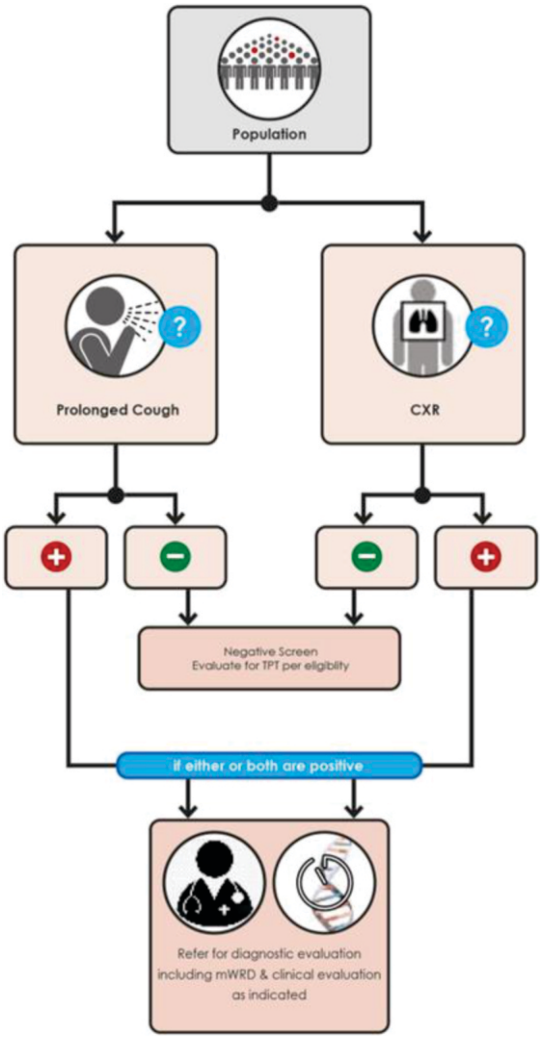
2.2.6.1. Contacts

Screening of household contacts of individuals with bacteriologically confirmed PTB is strongly recommended. Contacts of bacteriologically confirmed PTB have a high prevalence of TB, and a high risk of developing TB indicates urgent screening of this risk group. The goal of screening in this group is to identify TB disease early and to rule out TB accurately in those for whom active TB is not diagnosed. A highly sensitive algorithm is recommended and where feasible CXR because of its high sensitivity and specificity should be used for screening.

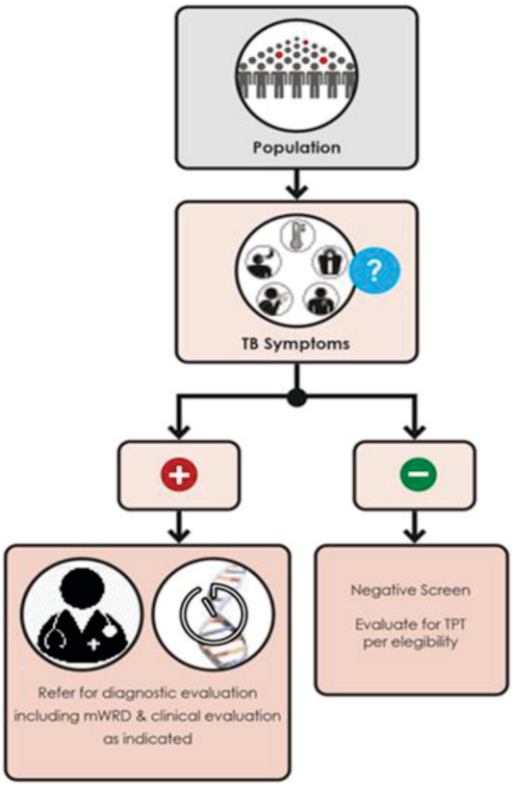
Contact investigation is centered around an index case which generally is the case identified initially but may not be the source case. Screening of contacts should ideally begin in the patient's household to ensure high coverage of this risk group. Thus, either transport of the patient to a nearby health facility or mobile CXR will be required to implement CXR-based algorithms in this risk group. Although a CXR-based algorithm is preferred for this group, a more feasible one may be used when CXR services are unavailable for the screening program.

Figure 6: *Recommended screening algorithm in Pakistan*

Screening algorithm for all setting HH contacts, Prisons, minors urban slums.



Screening algorithm for household contact in setting where Xray facility is not available



Out-of-household exposure is as likely to result in transmission as household exposure e.g. in school, workplace or social settings and in facilities such as correctional institutions and hospitals. Such sites (particularly social settings) are difficult to identify and require knowledge of the local culture and behavioral patterns in order to focus contact investigations. 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.

2.2.6.1.1 Screening child contacts of patients with TB

Child contacts are at high risk of TB disease, and the risk varies substantially by age. Newborn infants are at particularly high risk of infection with TB if the mother had untreated TB disease when they were born. An infant infected with TB has a very high risk of rapidly developing TB disease and dying. The risk of progression to TB disease is 20-50% among infants (<1 year) infected with *M. Tuberculosis* compared to 9% among older children and adolescents (5–14 years) in the 2 years after TB infection. The high risk of progression to TB disease and the associated high mortality rates underlines the importance of screening children exposed to close contacts 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

In young children, reduced playfulness or lethargy should also be included in symptom screening; cough may be absent. It is useful to examine growth charts regularly to determine whether a child has been losing weight or their weight has plateaued. A plateau in weight gain should be a warning sign for possible TB. In the latest review, a symptom screen in which a child has any of the symptoms of cough, fever or poor weight gain has a sensitivity of 89% and a specificity of 69% for TB disease (against a composite reference standard).

2.2.6.2 Adults and adolescents living with HIV

Since 2011, WHO has recommended that people living with HIV be systematically screened for TB disease. The recommendation is based on the high risk of this group for TB and mortality and a lingering gap in case detection in this population. 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.

Recent evidence indicates, however, that the accuracy of W4SS may be suboptimal for certain subpopulations living with HIV: It is relatively sensitive in outpatients not on ART (84%), indicating that W4SS is useful in finding people with TB among people who are starting HIV care, but the lack of specificity has implications for resources and rational use of diagnostic testing. The sensitivity of W4SS among outpatients on ART is relatively low, (53%), indicating that W4SS alone may not be sufficient to detect TB among people in regular ART care. CXR combined with symptoms is recommended for screening where available.

2.2.6.3 Miners

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. Large mines often have facilities on site to conduct CXR screening for employees; smaller, informal mines may have limited capacity and may have to use other providers while increasing capacity.

2.2.6.4 Prisoners

Given the high risk of transmission in this group, a highly sensitive algorithm beginning with CXR is preferred. Larger prisons and penitentiary institutions may have radiography capacity on site or can bring mobile vans for screening campaigns. In smaller institutions or locations where CXR capacity is not available, screening algorithms based on symptoms followed by mWRD may be acceptable until CXR services are available.

2.2.6.5 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.

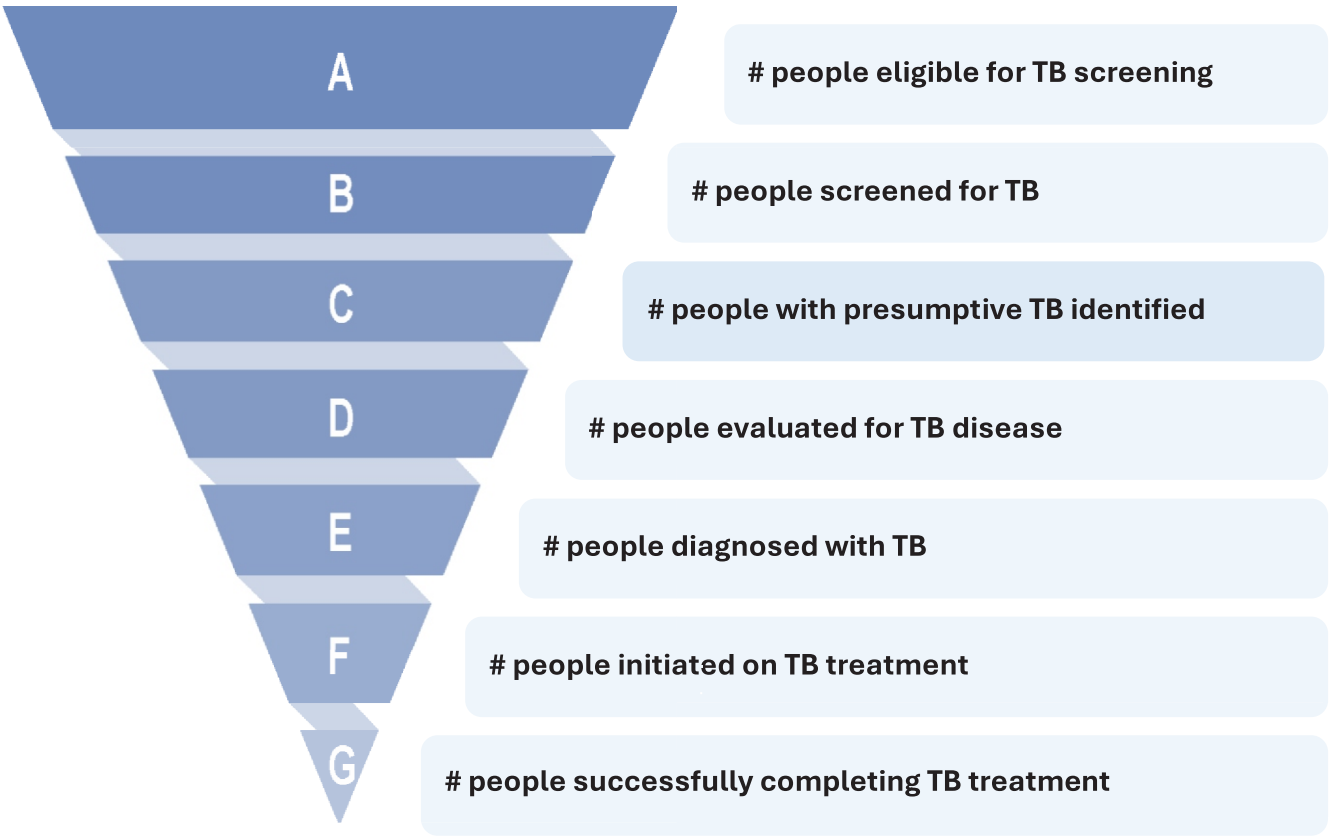
2.2.6.6 General population and communities with structural risk factors

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 to provide the highest yield in terms of maximizing case detection. Substantial work is usually required to take intervention activities into the field. Such an algorithm, however, requires substantial resources for implementation.

Screening for symptoms, although is much easier but is less sensitive and specific and has a smaller potential impact on population prevalence or transmission and is not recommended for screening in the general population.

2.2.7 *Monitoring of Screening initiatives*

Continued monitoring can help to assess the performance of the TB screening program. The following indicators should be considered for each targeted risk group[4]:Figure 7: *Indicators for TB screening*



Acceptability (B/A)
Screened positive (C/B)
Testing retention (D/C)
NNS and number necessary to treat (E/B) and tested (E/D)
Linkage to care (F/E)
Treatment success (G/F)

[4] https://iris.who.int/bitstream/handle/10665/340256/9789240022614-eng.pdf?sequence=1

Chapter 3

Management of TB Preventive Treatment

3. Management of TB Preventive Treatment

TB infection is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifested active TB. Currently, around 1/4th of the world's population is estimated to be infected with *M. tuberculosis*. Most of the infected individuals show no signs or symptoms of TB. Out of those infected 5–10% develop TB disease over the course of their lives and around 75% of people develop active disease within one year.

Prevention of active TB disease for high-risk groups by treatment of TB infection is a critical component of the WHO End TB Strategy[5]. The efficacy of currently available treatments ranges from 60% to 90%. Individuals infected with TB have a significantly higher risk of progression to active disease compared to the general population, and the benefits outweigh the harm. However, it is essential to rule out TB disease clinically and radiologically before starting TB Preventive Treatment (TPT).

3.1 Programmatic Management of TB Infection

Preventive treatment of M. tuberculosis infection should be selectively targeted for the population groups at the highest risk of progression to active TB disease, who would benefit most from the treatment of TB infection. To initiate TB preventive treatment, active TB need to be ruled out first. It is important to understand the difference between TB infection and TB disease to start preventive treatment.

3.1.1 Group Recommended for Preventive Treatment

Preventive treatment is recommended for two broad groups:

People with an increased likelihood of exposure to TB disease

a. Household contacts of people with bacteriologically confirmed TB:
   - Children below five years of age
   - Children five years and above, adolescents and adults
b. Persons who live or work in institutional or crowded settings, such as prisoners, health workers, recent immigrants from countries with a high TB burden, homeless people and people who use drugs.

People with elevated risk of progression from infection to TB disease

a. People living with HIV
b. Well-specified other high-risk groups which include,
   - patients initiating anti-tumor necrosis factor-α treatment
   - patients on hemodialysis
   - patients preparing for an organ or hematological transplant
   - patients on cancer chemotherapy
   - current and former workers in workplaces with exposure to silica dust

[5] https://iris.who.int/bitstream/handle/10665/331326/WHO-HTM-TB-2015.19-eng.pdf?sequence=1

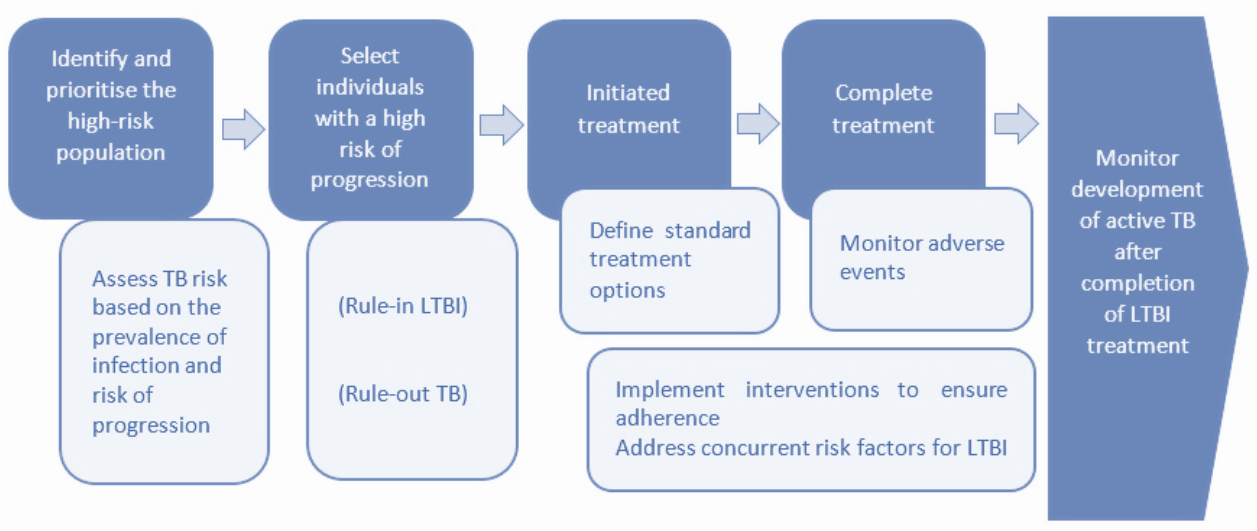
Table 13: *Differences between TB Infection and TB disease*

	TB Infection:	Active TB Disease:
Sickness	Does not feel sick	Usually Feels sick
Symptoms	Do not have any symptoms	Usually have one or more symptoms
Ability to spread TB	Cannot spread TB bacteria to others	May be able to spread TB bacteria to others
Risk of Progression	Are at risk for developing TB disease	
Duration	Can have latent TB infection for years	
Presence of bacteria	Have a small amount of TB bacteria in their body that are alive but inactive	Have a large amount of active TB bacteria in their body
Chest X-ray	Normal chest X-ray	May have an abnormal chest x ray,
TB Blood test (Interferon-gamma release assay-IGRA) and TB skin test	Usually, positive indicating TB infection	Usually, positive result indicating TB infection
AFB smear/Culture	No growth on culture, No AFB on smear	Positive culture AFB smear
Treatment	Treatment for TBI to prevent TB disease need to be considered	Need treatment for TB disease

3.1.2 Schematic Approach to the Programmatic Management of TB Infection

Management of TB infection involves a schematic and comprehensive package of interventions: Screen individuals at risk of TB infection, rule out active TB, initiate effective and safe preventive TB treatment, ensure adherence and treatment completion, monitor and evaluate the process.

Figure 8: *Schematic approach to programmatic management of TPT*



3.1.2.1 Exclude Active TB disease

Most persons, but not everyone, with TB disease have one or more symptoms of TB disease or abnormal chest Xray . All persons with either symptoms or abnormal Xray result should be evaluated for TB disease.

How to Rule out active TB Disease Before Starting TB Preventive Treatment

Two major groups of people, who should be systematically evaluated for TB disease and to rule out TB disease thoroughly before initiating TB preventive treatment are

Household contacts of pulmonary TB patients

The absence of

a) Any symptoms of TB
b) Abnormal CXR findings

may be used to rule out active TB disease among household contacts aged ≥ 5 years and other risk groups before preventive treatment.

People living with HIV

a) Adults and adolescents (>10 y) without current cough, fever, weight loss or night sweats are unlikely to have TB disease.
b) Infants and children (≤10 y) who have poor weight gain, fever or current cough or who have a history of contact with a person with TB needs further investigation before initiating TB preventive treatment

   Note: Chest radiography may be offered to people with HIV on ART and TPT given to those without abnormal radiographic findings.

TB Infection testing and treatment is NOT recommended to be systematically carried out in diabetes patients, tobacco smokers, people with harmful alcohol use or who are underweight unless they are included in one of the above high-risk groups.

3.1.2.2 Evaluation for TB infection

A clinical diagnosis of TB infection can be established if a person has a history of contact with a Bacteriologically confirmed PTB patient and a medical evaluation does not indicate TB disease. The decision about treatment for TB infection shall be based on a person's chances of developing TB disease by considering their risk factors.

TB contacts, PLHIVs, and high-risk groups like patients initiating anti-TNF treatment, receiving dialysis, and preparing for an organ or hematological transplant, patients with silicosis do **not require a laboratory diagnosis of TB infection** (a positive TB Blood test /TB skin test) for initiation of preventive treatment. However, these groups must be evaluated to **exclude active TB disease** before the initiation of preventive treatment.

3.1.2.3 Laboratory tests for diagnosis of TB Infection

No tool allows direct measurement of *M. tuberculosis* infection in humans, and the diagnosis of TB Infection is based on a positive result by either of tests discussed below.

A positive TB skin test or TB blood test only tells that a person has been infected with TB bacteria. It does not tell whether the person has TB infection or has progressed to TB disease. Other tests, such as a chest x-ray and, bacteriological examinations are needed to rule-in or rule-out active TB disease.

Tuberculin Skin Test (TST)

TST is based on the detection of delayed-type hypersensitivity to Purified Protein Derivative (PPD), a mixture of antigens shared by several mycobacteria that gives rise to a skin reaction

TST is an affordable test and requires an injection into the skin by a trained professional. The patient has to make two visits, one for the injection and another 48-72 hours later for the reading of the results. A regular supply of PPD is required.

Tuberculosis Interferon Gamma Release Assays

Based on the principle that the T-cells of individuals who have acquired TB infection respond to re-stimulation with *M. tuberculosis*-specific antigens by secreting interferon-gamma.

Either a TST or IGRA may be used to test for TB infection however, active TB disease must be ruled out prior to prescribing preventive treatment. There is no strong evidence that one TB infection test should be preferred over the other. The choice will depend on the availability, cost, and health infrastructure.

However, these tests cannot accurately predict the risk of developing active TB disease, and are not mandatory nor recommended in resource-poor settings by WHO for initiating preventive TB treatment

Medical History:

Patient's history of TB exposure, infection, or disease
Consider demographic factors age, ethnic or racial group
Occupation that may increase the patient's risk for exposure to DS-TB or DR-TB
Medical conditions, such as HIV infection or diabetes that increase the risk of TB infection progressing to TB disease

Physical Exam:

Evaluate patient's overall condition
Other factors that affect TB treatment – Like such as HIV infection or other illnesses

Chest Radiograph:

Rule out the possibility of pulmonary TB

Test for TB Infection:

TST or IGRA can be used to test for TB infection*
New antigen-based skin tests for TB infection

**A test for TB infection is not a requirement for initiating TPT in people with HIV or individuals aged < 5 years in contact with people with TB disease.*

Testing for TB infection for any population group may be considered subject to the availability of resources but Testing for TB infection should not be a barrier to initiating TPT.

Testing for TB in BCG-Vaccinated People

Vaccination with BCG may cause a positive reaction to a TST, which may also be due to infection with TB bacteria.

TB blood tests (IGRAs), unlike the TB skin test, are not affected by prior BCG vaccination and are not expected to give a false-positive result in people who have received BCG.

3.2 Treatment options TB Preventive Treatment (TPT)

Among individuals infected with *M. tuberculosis*, there is a 5-10% risk of progressing to active TB. The risk is particularly elevated in children under the age of 5 years and people with compromised immunity. Many treatment regimens are available to treat TB infection in adults, adolescents and children. The WHO-recommended TB preventive treatment options include 6 or 9 months of daily H, 3 months of weekly rifapentine plus H (3HP), and 3 months of daily H plus R(3HR). Alternative regimens include 1-month of daily rifapentine plus H(1HP) and 4 months of daily R(4R). There is general consensus that the benefits of all the treatment options being recommended outweigh the potential harm. All WHO-recommended regimens could be used in any setting, regardless of TB burden, provided that the health infrastructure can ensure the treatment is given correctly without creating inequities, and that active TB can be excluded reliably before the initiation of treatment

The recommended options for preventive treatment in Pakistan are given in Table 14. Regimens containing isoniazid and rifampicin can be used in individuals of all ages however there are limited pharmacokinetic data to inform appropriate dosage and safety of rifapentine among children < 2 years of age and hence the 3HP regimen is recommended only for use in children two years and older. The benefits of 3HR for infants and children < 15 years of age outweigh the harm, given its safety profile, the higher rate of completion as compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid.

Table 14: *Recommended TB Preventive Treatment option in Pakistan*

Regimen	Duration	Medicine/Frequency	Age Group	Remarks
3 HP*	3-month	Weekly INH & Rifapentine	Adults and Children	Not recommended for pregnant and Children <2yrs
6H	6 -Month	Daily Isoniazid	Adults and Children	5 -15 mg/kg/day (not to exceed 600mg/day)
3HR**	3-month	Daily INH and Rifampicin	Children & Adolescent <15y	H: 5 -15 mg/kg/day (not to exceed 600mg/day) R: 10-20 mg/kg/day

*** The WHO agreed unanimously that the benefits of 3HP outweigh the harm, given the similar preventive efficacy, safer profile and higher completion rate of 3HP than isoniazid monotherapy.**

**** Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as a preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. *(Strong recommendation, low-quality evidence).***

Implementation consideration

The clinicians should consider the characteristics of the individual concerned to maximize the likelihood that treatment is completed as expected. Regimen choice is determined by considerations such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, availability and the individual's preferences.

All TB preventive treatment options can be self-administered. A RCT showed that self-administered treatment of the 3HP is not inferior to directly observed treatment. The requirement for a direct observation is not considered mandatory and could impose a significant barrier to the implementation, however people receiving TB preventive treatment should be supported through access to advice on treatment and management of adverse events at every encounter with the health services.

Drug interaction: Populations who may be more commonly at risk of drug-drug interactions from rifampicin include people with HIV on ART, women of childbearing age on contraceptive medicines (who need to be counseled about potential interactions and consider nonhormonal birth control while receiving rifampicin) and opiate users on substitution therapy with methadone.

3.2.1 Adverse Drug Reactions of TPT and their Management

Adverse Drug Reactions:

Patients on treatment for TB infection may develop following signs and symptoms or adverse drug reactions and should be reported to the health care provider,

Minor Side effects:

- Persistent tingling, numbness, or burning of hands or feet

Major side effects:

- Unexplained loss of appetite, nausea or vomiting, brown urine*, or jaundice (yellowing of skin or eyes)
- Persistent weakness, fatigue, fever, or abdominal tenderness
- Easy bruising or bleeding
- Blurred vision or changed vision

*Patients taking rifampin (RIF) or rifapentine (RPT) should be informed that they will notice an orange discoloration of urine and possibly other body fluids. This is normal.

Management of adverse drug reactions:

a. Inform the patient (parents/guardians of the pediatric patient) about possible adverse drug reactions and instruct them to seek medical attention when symptoms of possible adverse drug reactions first appear.
b. Conduct monthly evaluations for the findings of treatment-associated adverse events.

c. Order baseline liver chemistry blood tests (ALT or AST) for patients with specific conditions: HIV infection, liver disorders, postpartum period (≤3 months after delivery), injection drug usage, or taking medications with known possible interactions with either isoniazid or rifapentine.
d. Consider an individual baseline liver chemistry blood test for older patients, especially those taking medications for chronic medical conditions.
e. Conduct blood tests at the next clinical visit for patients with abnormal baseline testing and those at risk for liver disease.
f. Discontinue if a serum ALT/AST concentration is ≥5 times the upper limit of normal in the absence of symptoms or ≥3 times the upper limit of normal in the presence of symptoms.
g. Be vigilant for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia.
h. In case of a possible severe adverse reaction (e.g., hypotension requiring intravenous fluid support), discontinue treatment and provide supportive medical care.
i. In case of mild to moderate adverse reaction (e.g., dizziness), use conservative management (e.g., treat dizziness with rest, oral fluids), conduct clinical and laboratory monitoring, and consider continuing 3HP treatment under observation.

3.2.2 Contraindications of TPT

There are many contraindications to start the preventive treatment.

a. Acute and Chronic liver diseases
b. Hepatitis B & C
a. Regular and heavy alcoholism
b. Hepatic failure due to other causes
c. Pregnancy (for HP)
d. TB History
e. History of Adverse Drug Reaction (ADR) to Isoniazid (INH)

If any of the mentioned contraindications are noted in the contact's medical history, TB Preventive Treatment (TPT)should not be given.

Chapter 4

TB Diagnosis

4. Diagnosing TB

An important step in the pathway of TB care is rapid and accurate testing to diagnose TB. The microbiological detection of TB is critical because it allows people to be correctly diagnosed and started on the most effective treatment regimen as early as possible.

The WHO's End TB Strategy calls for the early diagnosis of TB and universal DST, highlighting the critical role of laboratories in the post-2015 era in rapidly and accurately detecting TB and drug resistance. The political declaration at the first United Nations (UN) high-level meeting on TB held on 26 September 2018 included commitments by Member States to four new global targets, which were subsequently renewed at the second UN high-level meeting on TB on 22 September 2023 One of these **targets is that at least 90 percent of the estimated number of people who develop TB are reached with quality-assured diagnosis and treatment in the 5-year period 2023–2027**[6].
The effective management of TB relies on the rapid diagnosis of TB, rapid detection of drug resistance and prompt initiation of an effective treatment regimen. Thus, there is a need for access to fast and accurate detection tests, and rapid and accurate DST for all people with TB.

4.1 Diagnostic tests with WHO recommendations

Conventional and new diagnostic methods are briefly described.

4.1.1 Conventional diagnostic tests for the diagnosis of TB

4.1.1.1 AFB microscopy:

Sputum-smear microscopy is a relatively insensitive test, with a limit of detection (LoD) of 5,000–10,000 bacilli per milliliter of sputum. Furthermore, sputum-smear microscopy cannot distinguish drug-susceptible strains from drug-resistant strains. However, sputum-smear microscopy still remains the primary diagnostic technique for evaluating individuals presenting with the signs and symptoms of TB at many centers. WHO recommends that TB program should transition by replacing microscopy with mWRDs that detect MTBC as the initial diagnostic test.

4.1.1.2 TB Culture:

It is the current gold standard method for the bacteriological confirmation of TB using commercially available liquid media. However, use of culture as a primary diagnostic test is not feasible because of the cost, the infrastructure requirements (biosafety level 2/3 or TB containment laboratory) and the long time required to generate results (1–3 weeks for a positive result and up to 6 weeks for a negative result).
Recommendation on use of conventional methods: AFB microscopy and culture are recommended to remain necessary to monitor response to treatment. Culture is still important in the diagnosis of pediatric, HIV and extrapulmonary TB from paucibacillary samples, and in the differential diagnosis of non-tuberculous mycobacteria (NTM) infection.

4.1.1.3 Species identification:

The culture process can result in the growth of many of the *Mycobacterium* species. Laboratory confirmation of TB requires testing of the recovered mycobacteria using a species identification test.

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[6] https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/featured-topics/un-declaration-on-tb#:~:text=On%2022%20September%202023%2C%20at,time%2Dbound%20targets%20and%20actions

Species identification to definitively identify MTBC is particularly important before initiating phenotypic DST (e.g. Capilia TB-Neo® from Tauns Laboratories, Numazu, Japan; TB Ag MPT64 Rapid Test© from SD Bioline, Kyonggi-do, South Korea; or TBcID© from Becton Dickinson Microbiology Systems, Sparks, USA).

4.1.1.4 Indirect Phenotypic DST:

DST on solid (LJ, 7H10 agar, 7H11 agar) and liquid media (7H9 broth, BACTEC Mycobacterial Growth Indicator Tube™ [MGIT] system) is reliable and reproducible, and it remains the reference standard for many anti-TB drugs.

Reliable phenotypic DST methods are available for Rifampicin(R), Isoniazid(H), Fluoroquinolone(FQs), Pyrazinamide(Z), Bedaquiline(BDQ), Linezolid(LZD), Amikacin(AMK), Streptomycin(STR), Clofazimine(CFZ), Delamanid (DLM), Pretomanid(Pa) and Cycloserine(CS). Phenotypic DST is not recommended for Ethambutol(E), Ethionamide (ETO), Prothionamide(Pto), Para-aminosalicylic acid(PAS), imipenem-cilastatin and meropenem.

4.1.2 WHO-recommended new test for detection of TB and DR-TB

This section provides brief descriptions of WHO-recommended technologies for the detection of TB and DR-TB. The WHO-recommended diagnostics tests have been reorganized to clearly delineate their intended use, as per the recommendations.

- initial tests for diagnosis of TB with drug-resistance detection
- initial tests for diagnosis of TB without drug-resistance detection
- follow-on diagnostic tests after TB confirmation

4.1.2.1 Initial diagnostic tests for diagnosis of TB with drug-resistance detection

These are broadly grouped as WHO-endorsed rapid diagnostics (WRDs); these are defined as diagnostic tests that employ molecular- or biomarker-based techniques for the diagnosis of TB. The newer, rapid and sensitive molecular tests recommended for the initial detection of MTBC and drug resistance are designated as mWRDs.

Xpert MTB/RIF Ultra assay

The Xpert MTB/RIF assay is a cartridge-based automated test that uses real-time polymerase chain reaction (PCR) on the GeneXpert platform to identify MTBC and mutations associated with RIF resistance directly from sputum specimens in less than 2 hours. The Xpert MTB/RIF Ultra assay (hereafter called Xpert Ultra) was developed to improve the sensitivity and reliability of detection of MTBC and RIF resistance and it uses the same GeneXpert platform as the Xpert MTB/RIF test.

To address sensitivity, Xpert Ultra uses two multicopy amplification targets (IS6110 and IS1081) and a larger PCR chamber; thus, Xpert Ultra has a lower LoD than Xpert MTB/RIF (16 colony forming units [cfu]/mL and 131 cfu/mL, respectively). At very low bacterial loads, Xpert Ultra can give a “trace” result, which is not based on amplification of the rpoB target and therefore does not give results for RIF susceptibility or resistance. An additional improvement in the Xpert Ultra is that the analysis is based on melting temperature (Tm), which allows for better differentiation of resistance-conferring mutations.

The recommendations for Xpert MTB/RIF has been superseded by the Xpert MTB/RIF Ultra. Xpert MTB/RIF has been discontinued globally and will not be available in 2024 except in a few selected countries (e.g. India and the USA).

WHO recommends use of Xpert ULTRA as initial diagnostic test for TB and for detection of RIF resistance rather than smear microscopy or culture and phenotypic DST in

- In adults with signs and symptoms of pulmonary TB
- In children with signs and symptoms of pulmonary TB
- In adults and children with signs and symptoms of EPTB including meningitis

Truenat MTB, MTB Plus and MTB-RIF Dx assays

The Truenat MTB and MTB Plus assays use chip-based real -time micro-PCR for the semi-quantitative detection of MTBC directly from sputum specimens and can report results in under an hour. The assays use automated, battery-operated devices to extract, amplify, and detect specific genomic DNA loci. If a positive result is obtained with the MTB or MTB Plus assay, an aliquot of extracted DNA is run on the Truenat MTB-RIF Dx assay to detect mutations associated with RIF resistance. The assays are designed to be operated in peripheral laboratories with minimal infrastructure and minimally trained technicians, although micro-pipetting skills are required.

WHO recommends using Truenat MTB, MTB Plus in adults and children with signs and symptoms of pulmonary TB, as an initial diagnostic test for TB rather than smear microscopy or culture.

In adults and children with signs and symptoms of pulmonary TB and a Truenat MTB or MTB Plus positive result, Truenat MTB-RIF Dx may be used as an initial test for RIF resistance rather than culture and phenotypic DST.

Moderate complexity automated NAATs

The moderate complexity automated NAATs is a new class of NAATs class of tests that are also included as mWRDs which detect not only MTBC and RIF resistance but also INH resistance. These assays are less complex to perform than phenotypic DST and LPAs. After the sample preparation step, the tests are largely automated. Summary of overall performance for detection of TB and resistance detection to RIF and INH is given in table 15.

Table 15: ***Moderate complexity automated NAAT assay performance***

	Pooled sensitivity	Pooled specificity
TB detection	93.0% (95% CI: 90.9–94.7%)	97.7% (95% CI: 95.6–98.8%)
Rifampicin resistance	96.7% (95% CI: 93.1–98.4%)	98.9% (95% CI: 97.5–99.5%)
INH resistance	86.4% (95% CI: 82.8–89.3%)	99.2% (95% CI: 98.1–99.7%)

These assays offer high-throughput testing and are suitable for high workload settings, so have potential to be used in areas with a large population density or high TB prevalence. However, this class of tests is primarily for laboratory settings, and will require a reliable and rapid system for sample referral and result reporting.

WHO recommends, for people with signs and symptoms of pulmonary TB, using moderate complexity automated NAATs on respiratory samples for detection of pulmonary TB, RIF resistance and INH resistance, rather than culture and phenotypic DST. This recommendation is based on evidence of diagnostic accuracy in respiratory samples of adults with signs and symptoms of

pulmonary TB. The recommendation applies to PLHIV adolescents and children based on the generalization of data from adults.

Note: Equipment using Moderate complexity automated NAATs may /can be used for other diseases (e.g. severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], HIV, and hepatitis B and C) which could potentially facilitate implementation of TB testing on shared platforms.

4.1.2.2 Initial tests for diagnosis of TB without drug-resistance detection

TB-LAMP assay

The TB-LAMP assay is designed to detect MTBC directly from sputum specimens. This is a **manual assay** that provides results in less than 1 hour, does not require sophisticated instrumentation and can be used at the peripheral health center level, given biosafety requirements similar to those for sputum-smear microscopy. TB-LAMP does not detect resistance to anti-TB drugs. For the detection of TB in adults with signs and symptoms consistent with pulmonary TB, TB-LAMP has demonstrated a sensitivity of 78% (95% credible interval [CrI]: 71–83%) and a specificity of 98% (95% CrI: 96–99%) as compared with a microbiological reference standard.

WHO recommends use of TB-LAMP as a replacement test for sputum-smear microscopy for diagnosing pulmonary TB in adults with signs and symptoms consistent with TB. However, as TB-LAMP does not provide any information on RIF resistance, it is not recommended to replace the use of rapid molecular tests that detect both MTBC and RIF resistance with TB LAMP, especially among populations at risk of MDR-TB. Furthermore TB-LAMP should not replace the use of rapid molecular tests that have a higher sensitivity for the detection of TB among PLHIV who have signs and symptoms consistent with TB.

The urine LF-LAM

This is an immunocapture assay based on the detection of the mycobacterial **lipoarabinomannan (**LAM) antigen in urine; it is a potential point-of-care test for certain populations being evaluated for TB. The currently available urinary LAM assays have suboptimal sensitivity and specificity and are, therefore, not suitable as diagnostic tests for TB in all populations. Although the assay lacks sensitivity, it can be used as a fast, bedside, rule-in test for HIV-positive individuals, especially in urgent cases where a rapid TB diagnosis is critical for the person's survival. A positive LF-LAM result is considered to be bacteriological confirmation of TB in these people, A negative result does not rule out TB; therefore, it is recommended that LF-LAM should be implemented in parallel with mWRD testing among PLHIV.

Table 16: ***WHO recommendations on using urine LF-LAM for diagnosis of active TB in HIV-positive adults, adolescents and children***

Population	Setting	Clinical	CD4 counts	WHO Recommendation
HIV-positive adults, adolescents and children	In-Patient	Signs and symptoms of TB (pulmonary or extrapulmonary) with advanced HIV disease who are seriously ill	<200cells/mm3 Regardless of signs and symptoms	Yes
	Out-patient	Signs and symptoms of TB (pulmonary or extrapulmonary) Who are seriously ill	<100 cells/mm3, irrespective of signs and symptoms of TB.	Yes
		Without TB symptoms or not been assessed for TB symptoms	unknown CD4 cell count or with a CD4 cell count > 100 cells/mm3	No

Note: Anyone with signs and symptoms of pulmonary TB who is capable of producing sputum should have at least one sputum specimen submitted for an mWRD assay. LF-LAM results (test time <25 minutes) are likely to be available before mWRD results; hence, treatment decisions should be based on the LF-LAM result while awaiting the results of other diagnostic tests. LF-LAM may be used to assist in the diagnosis of TB but it should not be used as a triage test

4.1.2.3 Follow-on diagnostic tests after TB confirmation

These diagnostic tests are done as a follow on or reflex test once TB is confirmed for detection of additional drug resistance.

Xpert MTB/XDR Assay (Cepheid, Sunnyvale, USA).

This is low complexity automated NAATs. This test uses a cartridge designed for the GeneXpert instrument to detect resistance to INH, FQs, ETO and second-line injectable drugs (AMK, kanamycin and capreomycin). However, unlike Xpert MTB/RIF and Xpert MTB/RIF Ultra, which are performed on a GeneXpert instrument that can detect six colors, the new test requires a 10-colour GeneXpert instrument. The current WHO recommendations for Xpert MTB/RIF and Ultra cartridge use on GeneXpert 6-colour instruments are also valid for their use on GeneXpert 10-colour instruments. The Xpert MTB/XDR test provides results in less than 90 minutes.

Table 17: ***Xpert MTB/XDR assay pooled performance in detection of INH and Fluroquinolone***

	Pooled sensitivity	Pooled specificity
Isoniazid (INH)	94% (95% CI: 89–97%)	98% (95% CI: 95–99%)
Fluoroquinolone (FQ)	93% (95% CI: 88–96%)	98% (95% CI: 94–99%)

This test is intended for use as a **follow-on test or a reflex test** in specimens determined to be MTBC-positive; it offers the chance to improve access to rapid DST in intermediate and even peripheral

laboratories. The test can be used on culture isolates; However, the primary purpose of this test is to achieve rapid and early detection of resistance, and recommendations are for use directly on clinical specimens.

WHO recommends the use of MTB/XDR assay for detection of resistance to INH and second-line anti-TB drugs in people with bacteriologically confirmed pulmonary TB on sputum rather than culture-based phenotypic DST.

These recommendations are based on the evidence of diagnostic accuracy in the sputum of adults with bacteriologically confirmed pulmonary TB, with or without RIF resistance. The recommendations are extrapolated for adolescents and children based on the generalization of data from adults and also apply to PLHIV. The recommendations are extrapolated to people with extrapulmonary TB and testing of non-sputum samples are also considered appropriate, which affects the certainty. However, extrapolation was considered appropriate given that WHO recommendations exist for similar technologies for use on non-sputum samples (e.g. Xpert MTB/RIF and Xpert Ultra).
Note: There is an option to combine the 6- and 10-colour systems through a common computer, or to replace one 6-colour module in an instrument with a 10-colour module. However, these options are not yet offered to all countries.

Line Probe Assays (LPA)

LPAs are a family of DNA strip-based tests that detect mutations associated with drug resistance. They do this either directly, through binding DNA amplification products (amplicons) to probes targeting the most commonly occurring mutations (MUT probes), or indirectly, inferred by the lack of binding the amplicons to the corresponding wild-type probes.
LPAs are technically more complex to perform than the Xpert MTB/RIF assay; however, they can detect resistance to a broader range of first-line and second-line agents and provide mutation specific data for common variants. Testing platforms have been designed for a reference laboratory setting and are most applicable to high TB burden countries.
First-line LPAs: First-line LPAs (FL-LPAs) such as GenoType, MTBDRplus and NTM+MDRTB Detection Kit allow the detection of resistance to RIF and INH. WHO recommends using FL-LPAs for people with a smear-positive sputum specimen or a cultured isolate of MTBC, as the initial test instead of phenotypic DST to detect resistance to RIF and INH. These recommendations apply to both pulmonary and extrapulmonary sites.
Note: For populations with a high pretest probability of resistance to INH, conventional culture-based phenotypic DST for INH may still be used to evaluate a person with TB when the LPA result does not detect INH resistance.

Second-line LPAs: Second-line LPAs (SL-LPAs) such as the GenoType MTBDR*sl* test allow the detection of resistance to FQ and AMK. WHO recommends using SL-LPAs for a person with confirmed MDR/RR-TB, as the initial test, instead of phenotypic DST, to detect resistance to FQs and AMK.
Note: This recommendation applies to the use of SL-LPA for testing sputum specimens, irrespective of the smear status, and cultured isolates of MTBC from both pulmonary and extrapulmonary sites. Culture-based phenotypic DST may be useful in evaluating people with negative SL-LPA results, particularly in populations with a high pretest probability for resistance to FQs or AMK.

SL-LPA tests are also useful for detecting FQ resistance before starting therapy for Hr-TB.

Targeted next-generation sequencing (NGS).

This is a new class of tests – targeted next-generation sequencing (NGS) – which can be used for the detection of drug resistance to the broader list of drugs. This class of tests is based on technology that couples amplification of selected genes with NGS to detect resistance to many drugs with a single test. Also, since targeted NGS can interrogate entire genes to identify specific mutations associated with resistance, the accuracy may be better than that of existing WHO-recommended diagnostic tests (WRDs). In addition, new tests based on targeted NGS can detect resistance to new and repurposed drugs not currently included in any other molecular assays. Hence, this class of tests offers great potential to provide comprehensive resistance detection matched to modern treatment regimens.

4.2 National recommendation on use of diagnostic test for diagnosis of TB and drug-resistance

TB program at all levels should prioritize the development of a network of TB laboratories that uses a recommended tool for TB diagnosis (e.g. molecular methods and liquid culture), have efficient referral systems, electronic data system and diagnostics connectivity, standard operating procedures (SOPs), appropriate quality assurance (QA) processes, biosafety & biosecurity measures in place, sufficient human resources and storage capacity. These priorities should be comprehensively addressed in national strategic plans and should be adequately funded. National guidelines for the utilization of the new tool have been formulated, taking into consideration WHO recommendations and the accessibility of the tools in programmatic contexts. These recommendations include:

- For diagnosis of TB and detection of rifampicin resistance in patient with signs and symptoms of PTB and EPTB
- For detection of additional drug resistance in confirmed RRTB patient
- For detection of INH resistance in DSTB patient
- For monitoring treatment response in patients on TB treatment
- For detection for acquired /additional drug resistance during TB treatment

Table 18*: National recommendation for diagnosis of TB, detection of drug resistance and TB treatment monitoring*

Population	Recommendation	Specimen type	Remark
Recommendations for diagnosis of TB and rifampicin resistance in patients with signs and symptoms **of PTB and EPTB**			
Adults with signs and symptoms of pulmonary TB	Xpert Ultra should be used as the initial diagnostic test for TB and for detection of RIF resistance rather than smear microscopy or culture and phenotypic DST	Sputum or another respiratory specimen*	*bronchoalveolar lavage, gastric lavage or aspirates, nasopharyngeal aspirates and stool samples
Children with signs and symptoms of pulmonary TB		Sputum, gastric aspirate, Stool (<10yrs)	
Adults and children with signs and symptoms of extrapulmonary TB including TB meningitis		Tissue * (FNA, Excision biopsy) and body fluid**	*Tissue: Lymph node, bone, renal **Body fluid: CSF, Pleural and ascitic
		**Sputum should also be tested if screen positive for PTB.	** A high proportion of patients classified as EPTB have concomitant PTB. To identify concomitant PTB, routine screening of patients with EPTB for PTB is recommended.
Recommendations for detection of additional drug resistance in confirmed RRTB patients			
Adults and children diagnosed having confirmed Rifampicin resistant TB	MTB/XDR should be performed as follow-on or reflex test for rapid detection of FQ	Sputum or other non-sputum specimens	Testing can also be performed on non-sputum samples, provided RRTB is confirmed initially on testing by Xpert -Ultra
	Culture and phenotypic DST should be performed on all RRTB patient at time of second line treatment initiation (base line culture)		
Recommendations for detection of INH resistance in confirmed RSTB patient with History of previous TB treatment			
(Adults and children diagnosed having confirmed Rifampicin sensitive TB having history of previous TB treatment	For patients with History of previous ATT, rapid gDST (MTB/XDR or LPA) should be performed as follow-on test for rapid detection of INH and FQ resistance		if FL-LPA is performed, and Isoniazid resistance is detected, on FL LPA, SL-LPA should be performed for FQ DST
	For patient with HO of failure to FL-ATT both gDST (MTB/XDR or LPA) and pDST should be performed for detection of drug resistance and Possible RR missed by rapid gDST		Treatment should be initiated based on gDST results and modified once pDST results are available
Recommendations for monitoring treatment response in patients on TB treatment			
PTB+ and clinically diagnosed PTB patients	For PTB+ patient, AFB microscopy should be performed at the end of 2,5	Specimen (spot or morning)	If AFB smear is positive at 2 months in clinically diagnosed PTB patient,

	and 6 month. For Clinically diagnosed PTB at 2 months		MTB/RIF assay should be performed.
Adults and children having laboratory confirmed RRTB on second line TB treatment	AFB microscopy and culture should be performed every month	Sputum specimen	
Recommendations for detection for acquired /additional drug resistance during TB treatment			
PTB patient reported Sm+ve on 2-M Follow-up examination if • Bacteriological confirmed PTB at baseline with unknown rifampicin status • Clinically diagnosed PTB case at baseline	MTB/Rif assay should be performed for RR. Additionally, if INH resistance is suspected, Xpert XDR may be performed.	Sputum	
RRTB patients who have failed to convert by the end of 3rd month or revert after initial conversion while on DRTB treatment	Collect fresh specimen and refer for phenotypic DST	Sputum	tNGS if facilities available

4.3 TB Diagnostic Algorithms

Effective and efficient TB diagnostic algorithms are key components to ensure that people with TB are diagnosed accurately and rapidly and are promptly placed on appropriate therapy. This in turn, leads to better patient outcomes, reduced transmission and development of drug resistance is avoided.

The diagnostic pathway begins with a person identified as a presumptive TB person through assessment of signs and symptoms (passive case findings) or screened positive using an active approach. This section presents national recommendations on a set of three model algorithms that incorporate the goals of the End TB Strategy and the most recent WHO recommendations for the diagnosis and treatment of TB and DR-TB: Although the algorithms are presented separately, they are interlinked and cascade from one to the other.

Algorithm 1: is recommended for people with signs and symptoms of TB who are referred for diagnostic evaluation. Algorithms 2 and 3 follow on from Algorithm 1 based on the RIF result.

Algorithm 2 is recommended for those with confirmed RR-TB, and is aimed to detect resistance to second-line drugs

Algorithm 3 is recommended for those with confirmed RIF-susceptible TB at risk of having Hr-TB

4.3.1 Diagnostic Algorithm-1

This algorithm is recommended for people (adult, adolescent and children) with signs and symptoms of pulmonary and extrapulmonary TB who are referred for diagnostic evaluation to reach a bacteriologically confirmed diagnosis. It relies on mWRDs as the initial diagnostic tests. In Pakistan Xpert-Ultra which is most commonly available mWRD (or MC-NAAT available at few sites) is recommended as an initial test for all people.

Coverage of GeneXpert, Xpert MTB/RIF and Ultra in Pakistan

In Pakistan, the very first GeneXpert machines was installed in 2011 and Xpert MTB/RIF was introduced very soon after endorsement by WHO. Gradual expansion followed and currently more

than 450 health facilities are equipped and further expansion is under way. In Pakistan transition from Xpert MTB/RIF to Xpert Ultra started in 2017 and this was completed in 2022. Currently Xpert Ultra is the only assay available in programmatic settings for diagnosis of TB and Rif resistance.

Moderate complexity NAAT

It is available at a few large laboratories and is recommended for use as an initial test for diagnosis of TB and drug resistance. Most of these tools provide higher throughput and although some of these have minimal hands-on time, all have large infrastructure requirements; and thus, are suited to established laboratories with reliable sample referral networks.

IMPORTANT CONSIDERATION

Specimen referral and transport: To ensure equitable access to new diagnostic tools, for patients seeking health care from facilities lacking on site GeneXpert testing, an efficient referral and specimen transport system should be established, aiming to provide results within 48 hours of specimen collection.

Turnaround time: Results must be reported within 24 hours of specimen collection if Xpert testing facility is available on site, and within 48 hours for offsite facility.

AFB microscopy as initial diagnostic test:

In settings lacking on-site Xpert testing facilities and where reliable specimen referral and transport systems are not yet established or results are often delayed beyond 48 hours, AFB smears should be prepared from collected specimens. The same specimens should then be transported to the Xpert testing site. Specimens from all presumptive cases should be transported for Xpert testing. However, in constrained settings, priority should be given to 1) AFB smear-positive specimens, 2) AFB smear-negative specimens from patients with abnormal chest X-rays, and 3) any specimens from patients with immunocompromised conditions, extrapulmonary TB (EPTB), and children.

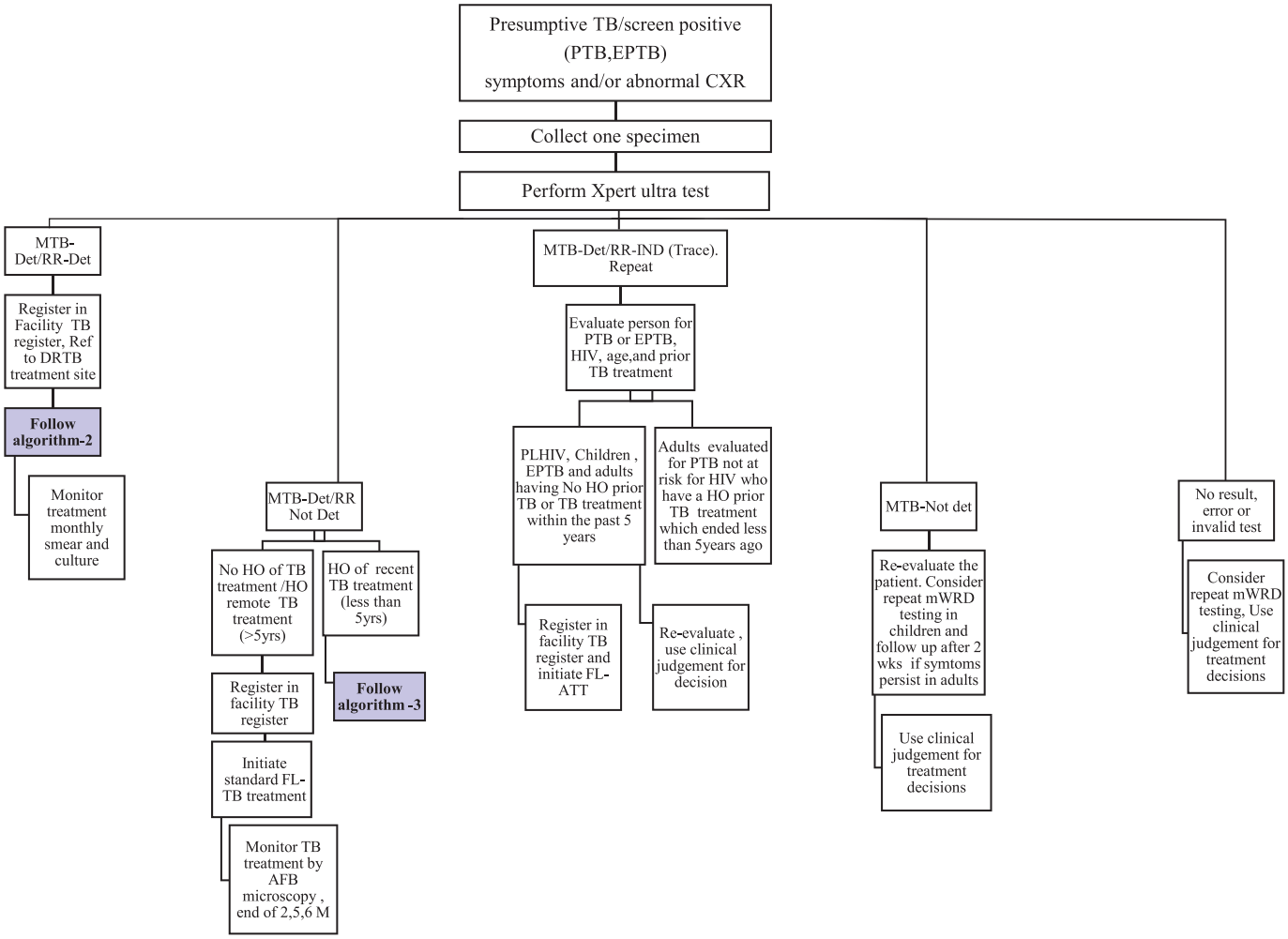
If the AFB smear is positive, patients should be initiated on first-line drugs immediately and once Xpert MTB/Rif results are available, treatment may be modified if necessary.

Repeat Testing: Repeat testing is not recommended other than in following conditions:

- People with signs and symptoms of TB reported “MTB Not Detected” on initial test, returning with persistence of symptoms after 2 weeks.
- Children with signs and symptoms of TB, reported ‘MTB not Detected” on initial test.
- Error/No Result/Invalid
- Bacteriological confirmed TB patients AT RISK OF DRUG RESISTANCE with indeterminate RIF results
- New patients reported RRTB having no history of TB treatment or any other risk of drug resistance.

All repeat testing should be performed on good quality specimen (preferably morning specimen) with extra care.

Figure 9: ***Diagnostic Algorithm 1***



*Specimen may be processed for culture to obtain isolate for DST. pDST may be considered for RSTB patient with history of previous TB treatment failure.

CXR with AI shall be used where available in routine setting to improve efficiency of Xpert ultra and cost

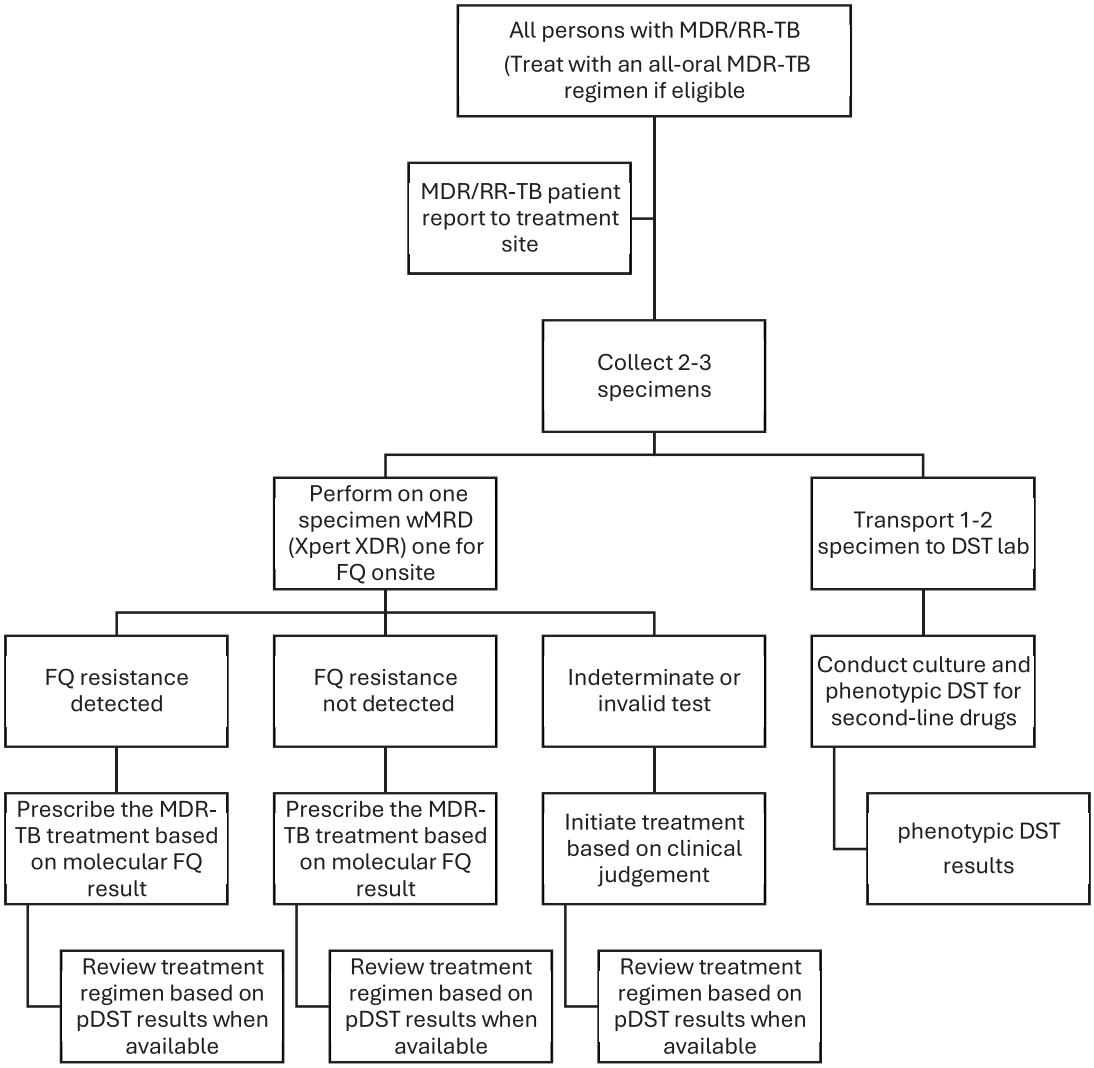
CXR preferably with AI should be used with Xpert ultra for screening program for high-risk group

Note: Evidence suggest that chest X-ray (CXR) can improved efficiency of using the Xpert MTB/RIF[1]: CXR and further clinical assessment can be used to triage who should be tested with the Xpert MTB/RIF assay to reduce the number of individuals tested and the associated costs, as well as to improve the pretest probability for TB.

4.3.2 Diagnostic Algorithm- 2

This algorithm is recommended for those with confirmed RR-TB, and is aimed to detect resistance to second-line drugs. The importance of DST before starting the preferred all-oral BDQ-containing MDR-TB regimen is important and stressed by WHO. Two of the key medicines in these regimens are BDQ and FQ. Currently, the only WHO-recommended molecular test to detect mutations associated with BDQ resistance is the targeted NGS test (Deeplex® Myc-TB from GenoScreen). Because of the limited availability of targeted NGS tests at this time, Algorithm 2 relies on the detection of mutations associated with FQ resistance using WHO-recommended molecular tests (a low complexity automated NAAT and SL-LPA) and phenotypic DST capacity for ATT medicines including BDQ, LZD, Pa, CS, CFZ and DLM, for which phenotypic methods, are accurate and reproducible

Figure 10*: Diagnostic Algorithm-2*



DST should be performed for all RRTB patient for Fluoroquinolone using rapid DST methods and Bedaquiline and Linezolid using pDST.

However, treatment for DRTB should not be withheld from a person because of a lack of complete DST results.

Availability of second line DST facilities in Pakistan

In Pakistan, as prevalence of FQ resistance is high (up to 40%), rapid DST to FQ is recommended.

Low complexity Xpert MTB/XDR to detect FQ resistance has been made available on priority to all DRTB treatment sites and further scale up is taking place in parallel with decentralization of DRTB treatment services.

Line Probe Assay (LPA) facility is also available at a few facilities but turnaround time is long and results are not available the same day. NTP does not plan for further scale up.

Targeted NGS is currently not available in program setting however once available it can be used to complement algorithm 2 for detection of drug resistance

Phenotypic DST; The use of low complexity automated NAATs to detect FQ resistance does not eliminate the need for conventional phenotypic DST, which are necessary for determining resistance to other anti-TB agents and for monitoring the emergence of additional drug resistance.

Reliable phenotypic DST methods are available for RIF, INH, FQs, BDQ, CFZ, Pa, CS, LZD, AMK and DLM. The initiation of treatment should not be delayed while awaiting the results of the phenotypic DST.

IMPORTANT CONSIDERATIONS

Specimens for DST:* Collect two and preferably three specimens from each MDR/RRTB patient at time of initiating treatment. Conduct molecular testing onsite and transport 1-2 clinical specimens to the appropriate testing laboratory for phenotypic testing.

Specimen referral and transport: An effective specimen referral and transport mechanism should be established between treatment site and culture. Specimens should be immediately refrigerated after collection and should be transported the same day in cold chain with the aim that specimen is processed for culture within 72 hours of collection.

Indirect Drug susceptibility testing: All culture isolates should be identified for MTBC before performing DST. Phenotypic DST should be conducted for each of the drugs included in the treatment regimen for which there are accurate and reproducible methods.

If no results or invalid results were reported on initial testing, rapid molecular test can be performed on culture isolates for rapid FQ results.

Culture and DST laboratories should establish the capacity to store all culture isolates from RRTB patients. If resistance to an individual drug (e.g. BDQ) is suspected and DST for these drugs is not available in the particular setting, isolates should be shipped to the NRL for DST.

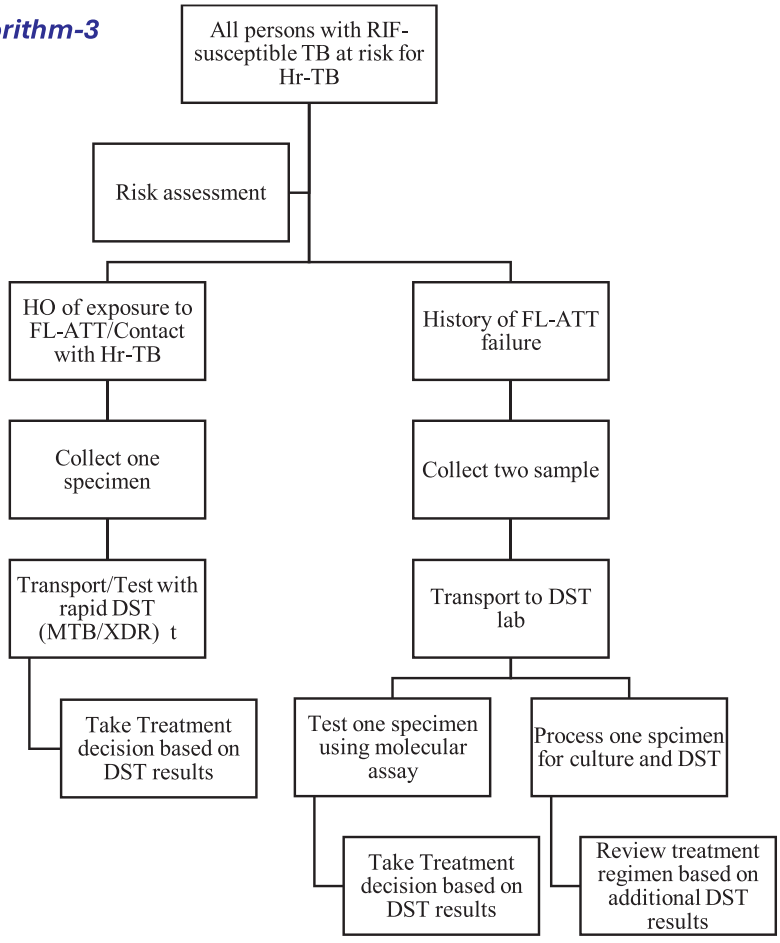
Monitoring treatment response: If the patient fails to convert by three months, second-line treatment response should be monitored every month by AFB smear and culture.

4.3.3 Diagnostic Algorithm 3

It is recommended for individuals with RIF-susceptible TB at risk of having HR-TB to detect resistance to INH and FQ. National guidelines recommend that TB Rapid molecular assay should be performed to detect resistance to INH in the patient

- Diagnosed with RIF-susceptible TB having a recent history of previous treatment (5yrs).
- Having a history of contact with a Patient known to have HR-TB.
- Who are not responding to first-line treatment and continue to be smear positive after 2 months or more of treatment, and those who experience treatment failure.
    - Decentralized molecular testing is preferred, and any of the existing WHO-recommended tests that detect resistance to INH and FQ may be used. FQ testing is mandatory and FQ should be added to treatment only if FQ is susceptible.

Figure 11*: Diagnostic Algorithm-3*



Phenotypic DST can provide information of resistance to other drugs and can also help detect RR missed by rapid molecular assay. However, as pDST capacity is limited, national guidelines currently recommend pDST for treatment failures of FL-ATT.

However, when available the ability of *targeted NGS* tests to detect mutations associated with resistance to many anti-TB drugs could be particularly useful for people at high risk of having DR-TB (e.g. people in whom therapy have failed).

Chapter 5

TB Treatment

5. TB Treatment

TB treatment is focused on curing the individual patient and minimizing the transmission of *M. Tuberculosis* to others. Thus, successful TB treatment benefits both the individual patient and the community. The objectives of TB treatment are:

- To rapidly reduce the number of actively growing bacilli in the patient, thereby decreasing the severity of the disease, halting transmission of *M. Tuberculosis* & preventing death
- To eradicate populations of persisting bacilli in order to achieve a favorable cure
- To prevent the emergence of drug resistance

It is imperative that people who have TB disease are treated, take ATT drugs in proper dosage exactly as prescribed and complete the treatment. If drugs are stopped or are not taken in proper dosage, patient can become sick again, and the TB bacteria that are still alive may become resistant to the drugs.

5.1. General Principles of TB treatment

5.1.1. Combination antimicrobial therapy for TB treatment

Large bacterial populations contain a small fraction of naturally resistant mutants (10^{-6} to 10^{-8}) that are resistant to any particular anti-TB drug. When the bacterial population is exposed to 1 or 2 drugs, the sensitive bacteria are killed, but resistant mutant bacteria survive, which subsequently multiply and replace the susceptible bacterial population, leading to drug resistance. However, when the bacterial population is exposed to a combination of four anti-TB drugs, the majority of the bacterial population, including mutant bacilli, is killed.

Thus, a combination of four drugs is used for treatment of TB during the initial phase for first two months and subsequently with 2 drugs during the continuation phase.

5.1.2. Universal DST

TB treatment should be based on susceptibility results. Rifampicin is a key drug in the treatment of drug-susceptible TB. It is therefore strongly recommended that all bacteriologically confirmed TB should be tested for drug susceptibility, at least for rifampicin, before/at the time of TB treatment initiation. Rifampicin testing at the start of treatment ensures that the patient is timely prescribed an effective treatment allocation. New rapid diagnostic has made this possible, mWRD (Xpert-Ultra) is widely available in Pakistan allowing rapid TB diagnosis along with simultaneous rifampicin susceptibility results. Most of the bacteriologically confirmed TB patients diagnosed on Xpert will simultaneously have Rifampicin results. However, if patients are diagnosed on AFB microscopy where Xpert is not available on-site, it is strongly recommended that the specimen should be referred for Xpert testing for Rifampicin susceptibility.

It is strongly recommended that all bacteriologically confirmed TB should be tested at least for rifampicin-resistance before/at the time of TB treatment

Rapid molecular tests (Xpert MTB/RIF assay) offered free of cost, are strongly recommended to diagnose TB and Rifampicin testing in both pulmonary and extrapulmonary TB in all populations. However, further DST for new rifampicin sensitive TB patient is currently not recommended due to limited resources

For Rifampicin sensitive TB, patient with history of previous TB treatment it is recommended that clinical specimen should additionally be tested for INH and Fluoroquinolone (FQ) using rapid low complexity automated NAAT (MTB/XDR assay) or medium complexity Line probe assay (LPA). As prevalence of FQ resistance is higher than Isoniazid resistance in Pakistan it is strongly recommended that LFX containing treatment regimen for INH resistance should be prescribed after confirmation of FQ susceptibility.

5.1.3. Uninterrupted availability of quality assured TB Drugs:

Free of cost, uninterrupted availability quality assured TB drugs for complete course of TB treatment for every TB patient should be ensured.

5.1.4. Care and support during TB treatment

All TB treatment should be delivered following WHO-recommended standards, including patient-centered care and support, informed consent where necessary, principles of good clinical practice, and regular patient monitoring to assess regimen effectiveness and patient safety.

5.2. WHO-recommended options for treatment of DS-TB

The 6-month regimen has been the standard of care all over the world but efforts have been made to develop effective shorter regimens to treat DS-TB. The WHO-recommended three regimens for DSTB are as follows:

- The **6-month regimen (2HRZ (E)/ 4 HR)** comprises 2 months of isoniazid, rifampicin, pyrazinamide (Z) and ethambutol (E), followed by 4 months of isoniazid and rifampicin. This regimen is recommended in all patient populations. In children (usually defined as being aged <10 years), the inclusion of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV, [12] in settings with isoniazid resistance or in children living with HIV (CLHIV), but can otherwise be omitted, resulting in the 2HRZ/4HR regimen.

> **In Pakistan**, The WHO-recommended-6-month regimen for DSTB is recommended regimen for treatment of DS TB (Rifampicin sensitive TB).

- The **4-month regimen HPMZ** comprises 2 months of isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 2 months of rifapentine, isoniazid and moxifloxacin. This regimen is recommended for all those aged above 12 years, whatever the severity of TB disease. **In Pakistan**, due to high Fluoroquinolone resistance, this regimen is currently not recommended under routine program settings. However, regimen may be used under conditions of operational research in situations where DST for INH and FQ is conducted for all TB patients.

- **The 4-month regimen HRZ(E)** comprises 2 months of Isoniazid, Rifampicin and Pyrazinamide, with or without Ethambutol, followed by Isoniazid and Rifampicin for 2 months for those aged between 3 months and 16 years, with non-severe pulmonary or peripheral lymph node TB. The use of

ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV, in settings with isoniazid resistance[13] or in children and adolescents living with HIV (CALHIV).
NTP Pakistan does not recommend 4-month regimen for CHTB in routine program settings due to possible challenges in definitely concluding non- severe form of disease as this regimen is recommended only for non-severe PTB and peripheral lymph node. However, the treatment may be prescribed in settings where trained Pediatricians are engaged in CHTB care or in operational research settings.

Table 19*: WHO-recommended options for treatment of DSTB*

<table>
<tr><th>Regimen</th><th>0-3Month</th><th>3Months - 10Years</th><th>10-12 years</th><th>12-16 years</th><th>>16 years</th></tr>
<tr><td>2RHZ(E)/4HR</td><td colspan="2">Ethambutol should be added in setting with background prevalence of INH resistance or HIV infection or CLHIV</td><td colspan="3">Independent of disease severity or HIV status</td></tr>
<tr><td>2RHZ(E)/2HR</td><td></td><td colspan="3">Non-severe TB, >3KG, add Ethambutol in setting with background prevalence of INH resistance or HIV infection or CLHIV</td><td></td></tr>
<tr><td>2HPMZ/2HPM</td><td></td><td></td><td></td><td colspan="2">Independent of disease severity or HIV status</td></tr>
<tr><td rowspan="3">Additional factors to be considered if several regimens are possible</td><td></td><td colspan="3">Disease severity</td><td></td></tr>
<tr><td colspan="5">Patient or Family preference</td></tr>
<tr><td colspan="5">Access and cost of regimen component drugs</td></tr>
</table>

CALHIV: children and adolescents living with HIV; CLHIV: children living with HIV; DS-TB: drug-susceptible TB; HIV: human immunodeficiency virus; TB: tuberculosis.

Note: all the regimens envisage daily dosing of all medicines

In 2017, the WHO abolished the former Category II standard 8-month regimen (2HRZES/1HRZE/5HRE), which comprised an intensive phase of 3 months (2 months of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin followed by 1 month without streptomycin), followed by a continuation phase of 5 months with isoniazid, rifampicin and ethambutol. Prescription of 8-month regimen is no longer recommended in Pakistan and choice of the treatment decisions in previously treated TB patients should be based on DST results for RIF, INH and FQ.

5.3. Recommendation for DS-TB Treatment in Pakistan

It is recommended that all patients with DS-TB (without documented resistance to isoniazid and rifampicin) should be treated using the 6-month rifampicin-containing regimen 2HRZ(E)/4HR, which comprises isoniazid, rifampicin, pyrazinamide and ethambutol, for 2 months followed by isoniazid and rifampicin for 4 months.
Of these, Isoniazid, Rifampicin and Pyrazinamide are bactericidal and Ethambutol is bacteriostatic drugs.

New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR. This recommendation applies to
Bacteriologically confirmed rifampicin sensitive new PTB patients.
Bacteriologically confirmed new TB patient with unknown rifampicin status
Bacteriologically confirmed rifampicin sensitive and INH sensitive PTB patients regardless of history of previous TB treatment.
Clinically diagnosed PTB patient regardless of history of previous TB treatment.
Extrapulmonary TB (except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy)

5.4. Recommendation for Treatment of Rifampicin sensitive Isoniazid resistant TB (HR-TB)

As TB patients with history of previous TB treatment are at increased risk of drug resistance, rifampicin testing should be ensured in this group of patients and Rifampicin sensitive TB patients having history of previous TB should be further tested for isoniazid and fluoroquinolone resistance.

Note: Due to risk of higher drug resistance In TB patients with a history of previous TB treatment, every effort should be made for the bacteriological confirmation of TB and rapid drug susceptibility (>90%) for these patients. TB diagnosis without bacteriological confirmation in these groups should be allowed only for those with pulmonary or extrapulmonary lesions in whom specimens' collection is challenging and there is strong clinical evidence of active TB.

TB Patients should be treated based on DST results regardless of history of previous TB treatment. However, as currently, testing for INH resistance is recommended only for Previously treated TB patients, understandably HR-TB will be detected among this TB patients' group. However, recommendations for treatment of HR-TB will also apply to new TB patients subject to laboratory confirmation.

- Isoniazid resistant and Rifampicin-sensitive TB, shall be treated with HRZE + Levofloxacin for six months if FQ is sensitive or FQ resistance in not documented
- Isoniazid resistant and Rifampicin-sensitive TB should be treated with HRZE for six months if FQ is resistant.
- Bacteriological confirmed TB patient with unknown isoniazid susceptibility status having history of previous TB treatment (excluding relapse) shall be treated with 6RHZE

Note: All clinically diagnosed TB patients with history of previous TB treatment (including relapse) shall be treated with 6-month treatment for DS-TB. (2RHZE and 4RH)

5.4.1. Key considerations and Guidance for 6-month RS-TB Treatment

a) Eligibility

Any patient – whether a child or an adult – with DS-TB (Undocumented rifampicin resistance to Rifampicin and Isoniazid) is eligible for 2RHEZ/4HR regimen. The regimen is considered safe for pregnant women; it can also be used in children of all ages, although ethambutol can be omitted for patients who are HIV-negative or in settings1 with a low prevalence of HIV or isoniazid resistance.

Table 20*: Treatment regimens for Rifampicin-sensitive TB*

Regimen	Patient eligibility	Initial Phase	Continuation Phase
1	New TB case bacteriologically confirmed (Rifampicin sensitive or Rifampicin resistance not documented) New TB case clinically diagnosed Previously treated TB case having bacteriologically confirmed, Isoniazid Sensitive TB (laboratory confirmed) Previously treated Clinically diagnosed	2HRZE	4HR
2	Previously treated TB patient having Bacteriologically confirmed, INH resistant and FQ sensitive TB (laboratory confirmed) Previously treated TB cases having Bacteriologically confirmed, INH resistant (laboratory confirmed) with unknown FQ status.) Same recommendation applies to New TB patient with laboratory confirmed HR-TB	6HRZE + LFx	
3	Previously treated TB cases having Bacteriologically confirmed, INH resistant and FQ resistant TB (laboratory confirmed) Previously treated TB cases having Bacteriologically confirmed TB with unknown INH and FQ status. Same recommendation applies to New TB patient with laboratory confirmed HR-TB plus FQ resistant	6HRZE	

b) Drug susceptibility;

Where possible, it is best to ascertain susceptibility to the medicines used; National guideline recommends that all new bacteriologically confirmed TB patient should be tested for susceptibility to rifampicin and patients with history of previous TB treatment susceptibility to both Rifampicin and isoniazid (the most potent drugs in the regimen) should be performed and are particularly important. In patients with evidence of resistance to isoniazid or rifampicin, 2RHEZ/4RH should not be used; instead, a regimen recommended for HR-TB is recommended.

What if rifampicin susceptibility results are not available?

In settings where DST results are not available to guide the management of individual patients', history and clinical judgement should be used to make decisions on the empirical use of this regimen. This also applies to CHTB and EPTB where bacteriological diagnosis and drug susceptibility of TB in children is particularly challenging.

c) Composition and duration of the regimen 2HRZE/4HR

The National guidelines recommend treating people with DS-TB with a 6-month regimen composed of four first-line TB medicines: isoniazid, rifampicin, pyrazinamide and ethambutol. The regimen is a

combination of those four drugs (i.e. HRZE) for 2 months followed by isoniazid and rifampicin (i.e. HR) for 4 months, administered daily. For recommended dosages (Table 21).

In children (usually defined as being aged <10 years) ethambutol can be omitted, resulting in a 2HRZ/4HR regimen, however ethambutol should be used in the first 2 months of treatment in settings with a high background prevalence of isoniazid resistance (know HR-TB in Index TB) or HIV infection, or in CLHIV.

As a general rule, **Prolonging treatment beyond the recommended period of six months** has minimal benefits, provided the patient has taken the medication without interruption. The first 2 months of treatment, which includes four drugs, is usually enough for the strong bactericidal activity of this regimen to be effective.

d) Drug formulation and dosage

Fixed dose combination drugs (FDCs): Evidence suggests that FDCs with proven bioavailability are effective for TB treatment, reduces treatment failure and improve treatment adherence while minimizing adverse events and drug resistance. **The use of FDCs** is recommended as it is patient friendly due to lower pill burden. The FDC also has advantages over the individualized prescription of drugs, e.g., it reduces errors in prescription, thereby reducing the risk of development of drug resistance. FDC also provides programmatic benefits as estimation, order & supply of drug requirements is easier, simplifying supply chain management, reducing the occurrence of stock-outs, and facilitating drug delivery and prescription. FDCs are of additional benefits that it reduces the need for training in dosing and dispensing of medications. The dosages & duration of fixed dose combination (FDC) for each category of treatment are given in the table-21

Separate drug formulations

Separate drugs are prescribed in special conditions as use of FDCs lacks the flexibility, and may not always provide optimal dosing in all individuals. Availability of single drug formulations are essentially needed to manage adverse reactions to TB medications, when drugs are reintroduced one at a time.

Note: All TB program should collect information on special condition and frequency of adverse reaction to estimate need, forecast and procure quantity of loose or single drug formulations accordingly

Table 21: *Dosage and duration of FDC for RS-TB*

TB regimen		Duration	Weight band (kg)/ based FDC drug dose (Tablets)		
			30-39	40-54	55 & above
Bacteriologically confirmed RSTB OR B+ve R status unknown OR Clinically Diagnosed TB (new and Previously treated TB cases)					
2HRZE Initial Phase	HRZE (H 75mg + R 150mg +Z 400mg + E 275mg)	2 months	2	3	4
4HR Continuation Phase	HR (H 75mg + R 150mg)	4 months	2	3	4
	HR* (H 150mg + R 300mg)	4 months	1	1.5	2
Bacteriologically confirmed RSTB with INH resistance and FQ sensitive (laboratory confirmed) or FQ status unknown. (Previously treated or New TB)					
6HRZE+Lfx	HRZE (H 75mg + R 150mg + Z 400mg + E 275mg) + Levofloxacin 250mg	6 months	2	3	4
B+ve RS-TB with H resistance and FQ resistance (laboratory confirmed) (Previously treated or New TB)					
6HRZE	HRZE (H 75mg + R 150 mg + Z 400mg + E 275mg)	2 months	2	3	4
	HRZE (H 75mg + R 150mg + Z 400mg + E 275mg)	4month	2	3	4

*(H = Isoniazid, R = Rifampicin, Z = Pyrazinamide, E= Ethambutol, If HR (H 75mg + R 150mg) is not available, then use HR (H 150mg + R 300mg) + E (E400 mg)

Note: In situations where isoniazid susceptibility results are not available for a previously treated patient (excluding relapse) having bacteriologically confirmed Rif sensitive TB, the patient shall be treated for six months with RHZE regimen (6RHZE)

TB treatment prescription coding:

The standard code for anti-TB treatment uses an abbreviation for each anti-TB drug: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). The number at the front drug regimen represents the duration of treatment in months. Example, 2HRZE: Duration of this phase is two months and drug treatment are daily with isoniazid, rifampicin, pyrazinamide and ethambutol.

Dosing and preferred time for anti-TB drug intake:

Daily dosing is recommended as it is considered optimal to reduces the probability of selecting resistant mutants. Anti-TB drugs are best absorbed on an empty stomach, time for administration is a single daily dose in the morning (half an hour before breakfast) Is preferred and recommended

e) Patient support and Treatment adherence

To ensure optimal treatment adherence and minimize the acquisition of MDR/RR-TB It is critical to educate and ensure adequate treatment support in the context of patient-centered care. Implementing treatment support and care requires resources and should be budgeted.

Health education and counseling on the TB disease and treatment adherence should be provided to all patients initiated on TB treatment.

Directly Supervised Treatment: To avoid the risk of drug resistance, supervised treatment, including in-person and video-observed treatment (VOT), is recommended for the entire duration of treatment in both New and previously treated cases. It should be used for all patients with TB disease, including children and adolescents.

f) Treatment monitoring

Standard treatment monitoring should be ensured to assess the treatment response and any adverse events.

Malabsorption of drugs and drug–drug interactions can occur, especially in People with HIV or those with diabetes, in critical care or receiving concomitant medications. Anti-TB drugs may need to be temporarily suspended or stopped in case of severe drug intolerance or toxicity.

g) Periodic drug-resistance surveys (DRS) and ongoing surveillance

DRS should be performed for monitoring the impact of the regimen and the overall treatment program. NTPs and Provincial TB Control Programs (PTPs) should obtain and use country/province-specific drug-resistance surveillance to estimate the level of MDR/RR-TB

5.5. Treatment of Extra pulmonary TB

Treatment of extrapulmonary TB is similar to that of pulmonary TB, being centered around the 6-month 2HRZE/4HR regimen; however, the regimen can be prolonged up to 12 months for tuberculous meningitis, osteoarticular TB or other types of extrapulmonary TB, as decided by clinicians. Furthermore, extrapulmonary TB is usually more difficult to diagnose, and evaluation of its outcomes can be more challenging because of the absence of bacteriological evidence in most patients and the need for cross-sectional imaging; hence, there is little quality evidence on this type of TB.

Table 22: *Duration of treatment in Extrapulmonary TB*

Site of EP	Regimen	Total duration
Cervical lymph node & pleural effusion	2 HRZE / 4 HR	6 months
TB meningitis and bone TB	2 HRZE / 10 HR	12 months

The use of adjuvant steroids: Is recommended in the treatment of Extra pulmonary TB disease in patients with

- **Tuberculous meningitis**, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used. The dosage depends on strong recommendation, moderate certainty in the evidence. **Preferable to be treated by the neurologist.**

- **Tuberculous pericarditis**, an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence).

  Preferable to be treated by the Cardiologist

5.6. Treatment of DS-TB in special conditions

5.6.1. Pregnancy

Health workers in charge of TB treatment provision should ask women in childbearing age before initiating treatment whether they are pregnant. A pregnant woman with TB must be informed that successful treatment with a standard regimen is important for the successful outcome of pregnancy.

- All first-line TB drugs are safe during pregnancy.
- A pregnant woman with a previously treated TB must be managed in the same manner as any previously treated TB patient.
- All pregnant women with TB should receive B6 vitamin (pyridoxine) supplementation during treatment.

5.6.2. Breast Feeding

Female TB patients who are breastfeeding should receive a full course of TB treatment.

- All first line anti-TB drugs are compatible with breastfeeding and women taking them should safely continue to breastfeed.
- Timely and properly applied chemotherapy is the best way to prevent transmission of tuberculous bacilli to the baby.
- Mother and child should stay together and the baby should be given prophylactic Isoniazid for at least 6 months.
- **BCG vaccination of the newborn should be postponed until two weeks after the end of Isoniazid prophylaxis, if the newborn has not already been vaccinated**.

5.6.3. Oral contraceptives

Rifampicin interacts with oral contraceptive medications with a risk of decreased protective efficacy against pregnancy. In consultation with a physician, an oral contraceptive pill containing a higher dose of estrogen (50 ug) may be considered, or another form of contraception (barrier) may be used.

5.6.4. Older people

The occurrence of TB among older people is often related to the higher prevalence of comorbidities (e.g. diabetes, chronic renal impairment and smoking) in this age group. The main challenges to successful treatment among older patients include poor drug tolerance, adverse events and poor treatment adherence, all of which could potentially lead to unfavorable treatment outcomes.

The case-fatality rate is reported to increase with age and lower sputum smear conversion after the intensive phase of treatment in patients aged over 60 years. Gastrointestinal upset and hepatitis are reported as the most frequent adverse events in older people. Clinical attention should be paid to older patients undergoing pyrazinamide treatment, to rapidly identify and manage any adverse events that eventually appear. Guidelines from the American Thoracic Society consider the option of excluding pyrazinamide in patients aged over 80 years.

Ethambutol is excreted by the kidney. A low glomerular filtration rate (GFR) (i.e. <30 mL/minute−1) has a poor prognosis in the treatment of TB (81). In older people, the dose should be reduced

according to the estimated GFR, but the time between doses should also be increased, to ensure that high blood levels of the drug do not persist.

When prescribing TB treatment in older people, it is always important to evaluate potential interactions among the different drugs prescribed to manage comorbidities. Older individuals are likely to have several comorbidities and are therefore likely to be taking other medicines; hence, there is potential for drug–drug interactions. The interaction between the anticoagulant warfarin and rifampicin is especially problematic, and either heparin or a non-vitamin K oral anticoagulant are considerably safer. Other important interactions include those with statins, analgesics (e.g. celecoxib and losartan), oral antidiabetic medications, steroids, calcium channel blockers and theophylline. Among older people, particular care is also necessary to ensure correct adherence to the prescribed treatment within a multidisciplinary and patient-centered approach.

Implementation considerations

- Although the drugs used to treat DS-TB are generally well tolerated and are unlikely to cause adverse events among older people, monitoring of adverse events is important to ensure rapid notification and prompt management.
- Notification and prompt management.
    - Management of older people with TB involves a multidisciplinary approach, in view of the additional treatments that are often required to manage comorbidities and the potential need to adjust drug dosing. A TB consilium (body of advisors) to support the management of people with TB that is difficult to treat may be of help.
    - Considering age-related physical and psychological disabilities, supporting adherence, is an important management component when treating DS-TB in older people. Thus, collaboration with partners in the community, including family members, care-givers, health care workers, and welfare workers is essential.
    - Coordination of NTP with geriatric services may be relevant.

5.7. Supervision and monitoring of TB Treatment

5.7.1. Counseling and health education in TB

Counseling and health education should be provided to the patient and their relatives/treatment supporters. It is often necessary to conduct a counselling session for a patient in the presence of a treatment supporter. Health education should be provided continuously to stress the importance of regular drug intake and follow-up examinations.

5.7.2. Treatment Supervision

Regular supervision is required for the entire duration of treatment in both New and Previously treated cases to avoid the risk of drug resistance. Video observed treatment (VOT) can replace DOT when the video communication technology is available and can be appropriately organized and operated by health care providers and patients. Supervision ensures that the patient takes all the drugs prescribed and in the event of any adverse reaction are referred to the TB Care Facility for the

management of adverse events.

5.7.3. Treatment monitoring

Monitoring the progress of treatment and identifying any problems for example adverse drug reactions or delayed response to treatment that may arise during treatment of DS-TB which might require additional investigations to decide whether to continue the therapy or change the treatment strategy.

Although people with DS-TB are much less likely than those with MDR-TB to fail treatment, it is important to outline the principles of effective monitoring where drug-resistance and possible failure are suspected.

Regular clinical examination (with monitoring of body weight), CXR and laboratory monitoring make it easier to determine whether something is wrong and thus take rapid action.

All patients, their treatment supporters and health workers should ideally be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), slow clinical improvement, symptoms of adverse drug reactions or treatment interruptions. Patient weight should be monitored each month, and dosages should be adjusted if weight changes. When possible, radiological monitoring may also be useful. Regular clinical examinations should be performed by the treating physician.

A written record of all medications given, bacteriological response and adverse events should be maintained for every TB patient on the TB treatment card.

5.7.4. Clinical examination

The classic symptoms of TB, cough, sputum production, fever and weight loss generally improve within the first few weeks of treatment. Cough and sputum production can persist after sputum conversion in patients with extensive lung damage (often due to late diagnosis), but even in those with extensive lung damage, improvement is usually seen within 1–2 months of effective treatment.

Persistent fever, weight loss or recurrence of any of the classic symptoms of TB should prompt investigation for possible treatment failure, undetected resistance to one or more drugs in the current treatment regimen or untreated comorbidities. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure.

For adults, weight should also be recorded monthly, height is only recorded at the start of treatment to calculate BMI.

For children, height and weight should be measured monthly to ensure that they are growing normally. Normal growth rate usually resumes after a few months of successful treatment.

The **frequency of clinical visits** depends on the patient's clinical condition and evolution. **On average, for an outpatient with no specific problems, clinical examination is preferably done every week during the first month and once per month thereafter if the patient is stable.** More frequent clinical examinations may be necessary, depending on the clinical condition of the patient.

At every visit, the patient should be asked about the occurrence of adverse events; any potential difficulties in treatment adherence should be discussed with the patient and their treatment supporter. Clinical visits should coincide with bacteriological and clinical laboratory examination schedules, to limit time and transportation constraints for the patient.

For extrapulmonary DS-TB, it is essential to monitor the clinical evolution to assess the treatment response because, in general, bacteriological monitoring is difficult.

5.7.5. Chest radiography

In the first few months of treatment, the patient's chest radiograph may appear unchanged or show only slight improvement. Although there are no formal recommendations, subject to the availability of CXR facilities and patient clinical condition, treating physician may consider to undertake CXR at baseline, at the end of the second month of treatment and at the end of treatment, to document progress and to use for comparison if the patient's clinical condition changes at any time after the achievement of treatment success. A chest radiograph at the end of treatment is also useful to optimally manage TB pulmonary sequelae after treatment

For extrapulmonary TB (in particular TB of the bone or joint), both radiographic examination and computed tomography (CT) can provide information on the evolution of the disease. However, some changes detected by CXR may never return to baseline; hence, the response often needs to be evaluated based on both clinical and radiographic findings. In contrast to pulmonary TB treatment, it is difficult to define what constitutes a cure in extrapulmonary TB.

5.7.6. Bacteriological examination

Response to treatment in pulmonary TB patients is monitored by bacteriological sputum smear examination. For pulmonary DS-TB, the most important evidence of improvement is conversion of the sputum smear.

For extrapulmonary TB, during the monitoring period sputum smears can be performed only if the patient develops pulmonary signs, or in the rare situation when materials valid for microbiological examinations are collected from the extrapulmonary site.

All PTB patients, including bacteriologically confirmed and clinically diagnosed DSTB, treatment should be monitored by sputum smear microscopy.

- For Bacteriologically confirmed PTB patients, sputum smear microscopy should be performed at the end of the second, fifth and sixth months of treatment and the sputum results recorded in TB01 & TB03.
- For Clinically diagnosed PTB patient, sputum smear microscopy should be performed at the end of second month of treatment. Those with sputum smear negative at 2 months need no further sputum monitoring. They should be monitored clinically; body weight is a valuable progress indicator.

Table 23*: Monitoring treatment response in a TB patient*

Supervised Treatment for Compliance			
Type of Patient	**Method**	**Frequency**	**Recording / remarks**
All TB patient	Supervised Treatment and VOT	Daily	TB treatment card
Clinical examination			
ALL TB patients PTB /EPTB (Bacteriological confirmed and clinically diagnosed)	Clinical symptoms,	At the baseline and then monthly.	TB treatment card/ If clinically condition is not improving correlate with CXR and Lab results
	Body weight	At the baseline, then monthly for all.	TB treatment card/ Dosages should be adjusted if weight changes
	Height	At the start of treatment for all to assess BMI. Monthly for children to assess growth.	
All PTB patients (new and previously treated)	CXR	Optional: At baseline, end of second month and end of treatment	Optional subject to availability of facility and clinical condition of patient
Bacteriological examination for treatment monitoring			
All PTB patients (new and previously treated)	*AFB -microscopy (sputum)*	For Bacteriologically confirmed PTB perform AFB microscopy at Follow-up Month 2,5,6	Record AFB microscopy results in TB treatment card /and TB register
	AFB -microscopy (sputum)	For clinically diagnosed PTB perform AFB microscopy at Follow-up Month 2	Record AFB microscopy results in TB treatment card /and TB register
	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 0M	Record results in TB card and TB register
		1)follow up smear is positive in clinically diagnosed PTB	
All TB patient if the patient does not improve clinically, or at any other time if failure is suspected because of possible drug-resistance	Culture and DST	At the end of the second month of treatment and at the end of treatment	

A positive sputum smear at the end of the second month may indicate any of the following:

- Even with good treatment response, non-viable bacteria remain present and are visible by microscopy.
- Resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load (this often occurs in cases of late diagnosis); and
- A poor treatment response because of one of the following reasons:
  - Poorly supervised initial phase of therapy and poor patient adherence.
  - Suboptimal quality of anti-TB drugs
  - Sub optimal doses of anti-TB drugs
  - Comorbid conditions that interfere with either adherence or treatment response (e.g. diabetes or cancer);
  - Undetected DR-TB that is not responding to first-line treatment; or
  - Suboptimal absorption of, one or more anti-TB drugs

What to do if one or more sputum smears are positive after 2 months?

The presence of one or more sputum smear results that are still positive after 2 months usually indicate the presence of dead bacilli; If patient is clinically and radiologically improving, the treatment should be continued.
In some cases, it might be due to undetected resistance to one or more drugs.
If the patient is not improving clinically and radiologically, and drug-resistance or potential failure is suspected, rapid diagnostic testing should be undertaken promptly, together with culture and DST, to provide a basis for any adjustment of the treatment strategy

Molecular tests such as Xpert MTB/RIF are not recommended for monitoring response to treatment. However, Xpert should be performed on follow up specimen reported AFB smear positive only in following situation,

- If clinically diagnosed PTB patient is reported, AFB smear positive at 2 months follow up
- If Xpert testing was not done at the baseline
- Xpert was done but rifampicin result was indeterminate because of Trace MTB results.

Although sputum smear is useful because of its much shorter turnaround time, sputum culture is much more sensitive for detection of ongoing active disease or treatment failure. Culture and DST should be performed for patients who remain smear positive, or for whom treatment failure is suspected. Where drug-resistance is suspected, DST needs to be performed – the core of which is to test for resistance to isoniazid, rifampicin and fluoroquinolone and, if possible, to undertake DST using rapid tests for second- line drugs.
It is usually not necessary to repeat DST within 2–3 months of the previous DST.
Sputum smear (and culture examinations) depend on the quality of the sputum produced, so care should be taken to obtain adequate specimens. Some patients may initially convert and later revert

to positive sputum smear, usually when undetected drug-resistance is present. In rare cases, malabsorption can be the cause.

5.7.6.1. Assessment of patients when treatment failure is suspected

Any patient not clinically responding to therapy after several weeks should be considered as being at risk for failure. In particular, patients should be considered as being at high risk for treatment failure if they had at least 3 months of full adherence to what was deemed to be an effective treatment regimen with quality-assured drugs, but show evidence of active disease, either clinical, radiographic or bacteriological (DST or culture) or reappearance of disease. The following steps are recommended in such a situation.

- **Confirm treatment:** The treatment card should be reviewed to confirm that the patient has fully adhered to treatment.
- **Look for undetected comorbidities:** Some undetected comorbidities mimic treatment failure through clinical and chest radiographic deterioration that occurs simultaneously with repeated culture-negative and smear-negative results. These comorbidities (e.g. NTMs, fungal infections, lung infections or a pulmonary malignancy) should be diagnosed and treated appropriately. Illnesses that may decrease absorption of medicines (e.g. chronic diarrhea) or may result in immune suppression (e.g. HIV infection) should also be excluded.
- **Review the bacteriological data**. Positive smears may be caused by the presence of dead bacilli and thus do not necessarily indicate treatment failure. Culture should be requested if failure.
- **Review the DST:** If there is evidence of acquired resistance to any drug, treatment failure is likely and a new regimen for DR-TB may need to be started promptly.
- **Review CXR:** If comparison of CXR at baseline and at the current time shows no improvement or deterioration of the CXR image, this may indicate failure of TB treatment.
- **Review treatment regimen:** The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If any resistance appears that was not present or evident previously, the patients should be managed as DR-TB or MDR-TB with a new regimen, and rapid action should be taken to ensure that adequate infection control measures are implemented.
- **Consider malabsorption:** Absorption of drugs is reduced in severely ill patients admitted to the critical care department with conditions such as central nervous system TB or acute respiratory distress syndrome (ARDS). In such cases, intravenous anti-TB treatment should be considered until the situation improves and a nasogastric tube can be used.

5.7.7. Follow-up of TB patients after completion of treatment

In routine setting Follow up after completion of treatment is not recommended for all TB patients who successfully completes full course of TB treatment. Post-treatment follow-up may be useful, for patients suffering from post-treatment sequelae. However, all patients, should be told to report back if symptoms recur.

Table 24*: Management of New TB Patients with Interrupted Treatment*

Length of interruption	AFB Smear		Xpert MTB/RIF		Further DST	Register again	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		No	Continue on same treatment and complete 60 doses of intensive phase
4-8 weeks	Yes	Pos/Neg	Yes	RS-TB	No	No	Re-Start again on 6-month DS-TB treatment (or HR-TB treatment if patient was on HR-TB before interruption)
				MTB-ND	No		
				RR-TB	Yes	Transfer /refer to PMDT treatment	Enroll on RR-TB treatment
>8 weeks	Yes	Pos/Neg	Yes	RS-TB	No	in same category as before (new or previously treated)	Re-Start again on 6-month DS-TB treatment (or HR-TB treatment if patient was on HR-TB before interruption)
				MTB-ND	No		
				RR-TB	Yes	Transfer /refer to PMDT treatment	Enroll on RR-TB treatment
Scenario 2: Length of treatment before interruption is more than one month							
<4 weeks	No	-	No	-		No	Continue on same treatment as before interruption and complete 60 doses of intensive phase
4-8 weeks	**Yes**	Pos/Neg	Yes	RS-TB	Yes-INH and FQ	as *Previously treated (Treatment after lost to follow-up)	Based on INH results, Re-Start on 6 -month treatment for DSTB or 6month treatment for HR-TB treatment
				MTB-ND	No		
				RR-TB	Yes	Transfer to PMDT /Register as RR-TB	Enroll on RR-TB treatment
>8 weeks	Yes	Pos/Neg	Yes	RS-TB	Yes-INH and FQ	as*Previously treated (Treatment after lost to follow-up)	Based on INH results, Re-Start again on 6 -month treatment for DSTB or 6-month treatment for HR-TB treatment
				MTB-ND	No		
				RR-TB	Yes	If RR+ Transfer to PMDT	Enroll on RR-TB treatment

5.7.8. Managing TB Patients Who Interrupt Treatment

Management of patients after treatment interruption is based on review of information about treatment before interruption and current Xpert and smear results (Table-24) Record of the previous treatment (before interruption) is important to know:

- The patient's previous regimen type
- Length of treatment before interruption
- Length of interruption

5.7.9. Drug Interactions during TB Treatment:

Drug interactions can occur during TB treatment and potentially change the pharmacologic effects of another drug that is given concomitantly. Clinically significant drug interactions are seen mostly with Rifampicin, Isoniazid, and Fluoroquinolones. Elderly individuals with significant comorbidities and immune-compromised patients (e.g., HIV/AIDS patients) are at higher risk of developing drug interactions during TB treatment. To minimize drug interactions, it is advisable that drugs be administered 12 hours apart. Important drug-drug interactions of Rifampicin, Isoniazid and other TB drugs are shown in Table 25.

Table 25*: Drug Interactions during TB Treatment*

TB Drug	Drug category	Interactions
Rifampicin	Anti-hypertensive	Markedly reduces levels of Calcium channel blockers (Nifedipine, Amlodipine, Verapamil). Reduces levels of B-blockers (Propranolol, Carvedilol). Isolated reports of interaction with ACE inhibitors (Captopril, Enalapril, Lisinopril) but minor clinical significance. No interactions found with diuretics (Thiazides, Spironolactone, Furosemide).
	Analgesics	Increases clearance of paracetamol. Decreases levels of diclofenac. Reduces opioid levels. No interactions with aspirin and Ibuprofen.
	Antifungals	Markedly reduces serum concentration of antifungals. Serum rifampicin levels can also be reduced with concurrent use of ketoconazole.
	Antiretroviral agents	Reduces levels of Efavirenz (EFV), Ritonavir and Nevirapine. Increases clearance of Zidovudine. No interactions found with Didanozine, Lamivudine.
	Anti-epileptics	One report of increased level and toxicity of Carbamazepine when RH is given together. Reduces levels of phenytoin and Valporic Acid.
Isoniazid	Antacids	Reduces absorption with concurrent use of Aluminum hydroxide (Give INH at least one hour before the antacid).
	Carbamazepine	Increases levels of carbamazepine markedly and rapidly.
	Oral Contraceptive	Risk of contraception failure is low with INH use.

	Paracetamol	Potential toxicity of paracetamol even at normal dose when used with INH (more studies are needed).
	Phenytoin	Increases levels of Phenytoin with concurrent use of INH.
	Theophylline	Plasma level of Theophylline may be increased
Ethambutol and Pyrazinamide		May interact with thiazide diuretics to cause elevated serum uric acid levels.
Pyrazinamide		May interact with Allopurinol and Probenecid can cause elevated uric acid levels.
Fluoroquinolone		Increases serum Theophylline level. Increases anticoagulant effect of warfarin. Concurrent use with sucralfate and antacids containing aluminum, calcium or magnesium may reduce absorption of quinolones. Serum levels of Ciprofloxacin is reduced with concurrent use of Didanosine.

5.7.10. Monitoring of adverse drug reactions

Screening for adverse drug reactions of anti-TB drugs is essential part of follow-up at the TBMU. It is a very important component of the TB care. This is mostly done by interviewing patients and/or treatment supporters when they visit the TBMU. There are two main types of adverse events, major and minor.

Table 26: *Adverse Drug Reactions and Their Management*

Adverse-Drug Reaction	Drug(s) probable responsible	Management
Major		**Stop responsible drug(s) and refer to clinician urgently**
Skin rash with or without itching	Isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment, optic neuritis (other causes excluded)	Ethambutol, INH	Stop ethambutol
Thrombocytopenic purpura, shock, acute renal failure	Rifampicin	Stop rifampicin
Minor		**Continue anti-TB drugs, check drug doses**

Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to treating physician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 40–75 mg daily
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Twice or thrice weakly drug intake (including rifampicin) should not be used anymore in the treatment of TB.

Major Adverse Events: are those that give rise to serious health hazards. The adverse events occur in 5-10% of the patients treated for TB. In this case, all anti-TB drugs should be STOPPED immediately and TB patient should be referred to a hospital specialist.

5.8. Treatment Outcomes

The TB care facility is responsible for ensuring treatment adherence and completion of registered TB patients and declaring outcome. The definitions for various treatment outcomes of the TB patients are given below:

Table 27*: New definition of TB 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 smear 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.

Chapter 6

TB in Children and Adolescents

6. TB in Children and Adolescent

Child is a person under 10 years of age and an adolescent is a person 10-19 years of age (inclusive). It is estimated that, 7.5 million children and young adolescents aged under 15 years are newly infected with *M. tuberculosis* each year.
Evidence from difference studies evaluated in a systematic review and meta-analysis reveal

- 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.
- This study found that children aged 2–5 years had an equally high risk of developing TB within 2 years (19%).
- 83% of all children aged under 5 years and 61% of children and adolescents with TB infection who developed TB disease do so within weeks of the initial contact investigation
- The effectiveness of TPT to prevent the development of TB disease is estimated at 91% for children and adolescents with TB 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,

Further, infants and young children, especially those aged under 2 years, are at higher risk of developing disseminated disease and TB meningitis (TBM), which are associated with high morbidity and mortality[7].
Adolescents with TB usually present with infectious TB disease, as typically seen in adults e.g., with cavities on chest X-ray (CXR) and bacteriologically confirmed disease[8].
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. Contact investigation to identify children, adolescents and other household members with TB disease and to identify those who will benefit from TPT should be a standard component of all TB program.

6.1. TB Screening and Contact Investigation

This chapter provides implementation guidance based on WHO recommendations on TB contact investigation and screening that apply to children and adolescents. 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.

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[7] Marais B. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(4):392–402.

[8] Roadmap towards ending TB in children and adolescents. Geneva: World Health Organization; 2018 (https:// apps.who.int/iris/handle/10665/275422, accessed 1 December 2021).

- 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).
- TB exposure usually follows household or other close contact with a person (usually an adolescent or adult) with bacteriologically confirmed PTB.
- If the index case is a child, it is recommended that contact investigation and screening include efforts to identify the likely source of infection. This is known as "**reverse contact investigation**" or "source case investigation."
- 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).

6.1.1. TB screening approaches in children and adolescents

National Guideline recommends screening for children and adolescent who are close contact of person with Bacteriologically confirmed TB and those living with HIV.

6.1.1.1. TB screening in Children who are close contact of person with Bacteriological confirmed TB

Screening serves to identify children and adolescents who may have TB disease (presumptive TB) and who need further evaluation to confirm a TB diagnosis. It also helps to identify children and adolescents who are eligible for and could benefit from TPT.

Any child aged under 10 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 are given in Table 28.

Symptom screening

Recommended symptoms for screening are given in Table 26. 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.

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.

Table 28*: Recommended Screening Tools*

	Children who are close contact of person with Bacteriological confirmed TB	Children living with HIV
Screening tool	Symptoms screen and/or cough	Symptoms screen
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

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, Milliary 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 posteroanterior and lateral views should be done.

Use of computer-aided detection software for interpreting CXR for TB is recommended by WHO as an alternative to human reading. This recommendation is currently limited to people aged 15 years and older, and more data should be collected to validate the performance of computer-aided detection software for TB in children.

CXR can be used in combination with symptom screening to screen for TB disease. CXR is not readily available in many locations, and travel to another location for CXR may not be feasible for caregivers, who may be unable to make time or to afford direct or indirect costs for travel, time, support or radiography services. Mobile CXR units may be used to reach populations with poor access, but these require training and financial and logistical support.

Newer digital X-ray machines emit a small amount of radiation, but the radiation risk to the patient is very low.

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 of TB infection but may be influenced by mechanisms unrelated to TB infection and give false-negative or false-positive results.

6.1.1.2. Screening children and adolescents living with HIV

Children living with HIV have a high risk of rapid progression to severe disease and death if a diagnosis of TB is missed. A child living with HIV is 3.5 times more likely to progress to TB disease than

Table 29*: Recommendation on BCG Vaccination*

Population	BCG vaccination	Remark
Neonates born to women with unknown HIV status	**YES**. should receive BCG vaccination.	
Neonates with unknown HIV status born to women living with HIV	**YES**. should be vaccinated	Provided they have no clinical evidence suggestive of HIV infection, irrespective of the mother's ART status.
Neonates diagnosed with HIV infection	NO. should **NOT** receive BCG at birth	Vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable
Neonates born to women with bacteriologically confirmed PTB who do not have TB symptoms	**NO**. should not receive BCG. Instead, they should receive TPT after exclusion of TB disease. If the infant remains asymptomatic and is HIV-negative, BCG vaccination should be provided using a normal infant dose **2 weeks after completion of the full course of TPT**.	The infant should be regularly followed up and monitored for the development of symptoms and signs suggestive of TB.
Children known to be living with HIV	should **NOT** receive BCG vaccination	Increased risk of developing disseminated BCG disease
Children known to be living with HIV on ART	**YES**. Should be vaccinated if clinically well and immunologically stable	immunologically stable children
Immunologically stable children: CD4% over 25% in children aged under 5 years. CD4 count of 200/mm^{3}or higher in children aged over 5 years. **In settings without access to CD4 testing**, immunological stability may be assessed clinically, based on the absence of new opportunistic infections and any other symptoms. If viral load testing is available, an undetectable viral load in combination with the child being clinically well without new opportunistic infections satisfies this requirement		

6.2.2. 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. A clinical algorithm based on screening for symptoms of TB, history of contact with a person with TB, HIV status, age, TB infection test results and abnormal findings on CXR is recommended.

- 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.
- If CXR is not available, a child can be started on TPT if TB disease is ruled out based on a negative symptom screen.
- The risk for TB disease after infection is particularly increased among young children and in people with immunocompromising conditions such as HIV infection, in whom disease progression is also more rapid, usually within 12 months of infection. Two broad at-risk child and adolescent populations that need systematic assessment for eligibility for TPT:
- all household contacts of bacteriologically confirmed TB patients especially children <5 years
- all HIV positive patients and
- adolescents with specific comorbidities or on specific treatment

6.2.2.1. TB Preventive treatment regimen

TPT recommended regimens for children and adolescents is given below in Table 30.

Table 30: *TPT recommended regimens for children and adolescents*

S. No	All Age Groups	
1	6INH	
2	3HP	
3	3HR	

6.2.2.2. TPT Follow-up

Children and adolescents on TPT should be reviewed every month for those on a 3-month regimen (e.g., 3HR or 3HP), and every 2 months for those on a 6-month regimen (e.g. 6H).

6.2.3. TB Infection and Prevention Control

To follow WHO-recommended protocols for TB infection prevention and control (explained in detail in chapter 10)

6.3. Diagnosis of TB in Children

Children and adolescents 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.

Table 31*: 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 X-ray	Children aged under 5 years: preferably Antero-posterior (AP) and lateral (Lat)
	Older children and adolescents: Postero-anterior (PA)
	CXR is useful to support the clinical diagnosis of PTB when TB is presumed and bacteriological testing is negative i.e. in very young children.
	acute pneumonia not responding to adequate course of antibiotics
Clinical examination	
Vital signs	Elevated temperature (fever) and increased respiratory rate.
Growth assessment	Poor weight gain in past 3 months. Severe Acute Malnutrition (SAM), especially if not responding to therapeutic nutritional treatment
Assessment for Pulmonary disease	
Auscultation and percussion	Usually normal but may reveal lung disease (e.g. crackles, bronchial breathing, fixed area of wheezing due to airway narrowing from enlarged lymph nodes) or Dullness, reduced breath sounds due to Pleural effusion. Persistent wheeze not responding to bronchodilators (especially if fixed and non-symmetrical).
Signs of respiratory distress	In children aged under 5 years: Signs of respiratory distress (chest indrawing, wheezing and oxygen saturation below 90%) are usually not due to TB but are important to guide clinical management.
Assessment for Extrapulmonary TB	Relevant EPTB e.g., Signs of meningitis, Lymphadenopathy
Laboratory investigation	
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)
HIV Screening	HIV screening as a baseline test for all age groups.
TST/IGRA	Not recommended

6.3.1. Pakistan Pediatric Association (PPA) recommended scoring chart for diagnosis of TB in children

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

Table 32: *Pakistan Pediatric Association revised scoring chart in 2016*

	1	2	3	4	5
Age	< 5 years				
Close Contact*	TB suggestive	Clinically diagnosed TB case (B-negative)	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

***History of cough** for more than 2 weeks in the household of a child (score 1), contact tracing is required. **B-ve TB patients** among the households (score 2), may or may not be receiving/completed anti-tuberculous treatment households. **B+ve TB patient** among the (score 3). May or may not be receiving/completed anti-tuberculous treatment.

****(Protein Energy Malnutrition/Severe acute malnutrition)** Use WHO-recommended Z. Scoring chart. **Not responding** to nutritional rehabilitation for 02 months.

*****Malignancies** like leukemia or lymphomas etc. **Immunodeficiency** diseases like agammaglobulinemia etc. **Chemotherapy /Immunosuppressive** therapy such as steroids for more than 2 weeks.

******Suggestive of TB:** Pulmonary Findings (unilateral wheeze, dullness), weight loss, hepato- splenomegaly, lymphadenopathy, ascites etc.

Strongly suggestive of TB: Matted lymph nodes, abdominal mass or doughy abdomen, sinus formation, gibbous formation, chronic mono arthritis, meningeal findings (bulging fontanel, irritability, choroid tubercle, papilledema).

*******Non-specific**, Ill-defined opacity or patchy infiltrates on chest X-Ray, marked broncho-vascular marking. **Suggestive of TB:** Consolidation not responding to antibiotic therapy, Para-tracheal, or mediastinal lymphadenopathy **Strongly suggestive:** Miliary Mottling, cavitation, Tuberculoma on CAT scan/MRI brain, collapse vertebrae etc.

Table 33: *Interpretation of PPA scoring chart*

Score	Interpretation	Suggested Actions
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**
7 or more	Probable TB	confirm (if possible)

6.4. 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.

Table 34: *Pulmonary TB treatment regimens by age group, disease severity and local epidemiology*

Age and severity *of TB	Duration and composition of treatment regimen[a]	
	Intensive phase	Continuation phase
Infants aged <3 months or weighing <3 kg		
PTB of any severity	2HRZ or 2HRZE [b]	4HR
Children and adolescents aged 3 months to <12 years		
PTB with non-severe TB disease	2HRZ(E)	2HR
Severe PTB	2HRZE [c]	4HR
Adolescents aged 12–<16 years		
Severe PTB	2HRZE [c]	4HR
Adolescents aged 16–<20 years		
PTB of any severity	2HRZE [d]	4HR

[a] *The standard code for TB treatment regimens uses an abbreviation for each medicine: isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). A regimen consists of two phases – the intensive and continuation phases. The number at the front of each phase represents the duration of that phase in months. For example, 2HRZE consists of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months.*

[b] *In settings with a high HIV prevalence and/or a high isoniazid resistance prevalence, ethambutol should be added to the intensive phase of treatment. High HIV prevalence settings are defined as HIV prevalence ≥1% among adult pregnant women or ≥5% among people with TB. Thresholds for low, moderate or high levels of isoniazid resistance prevalence are established by country NTPs.*

[c] *This regimen applies regardless of HIV prevalence and prevalence of isoniazid resistance.*

[d] *This regimen applies to older adolescents regardless of disease severity, HIV prevalence and prevalence of isoniazid resistance.*

** Non-severe TB is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern.*

National guidelines recommend that New WHO-recommended Short 4-month TB treatment for non-severe PTB and peripheral lymph node for children under 16 years TB **should not be used** in routine program setting and should be only be implemented under specialized pediatric care

Table 35*: Treatment regimens for extra-pulmonary TB*

Age and type of EPTB	*Treatment regimen* [a]	
	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 Meningitis [c]	**2HRZE**	**10HR**
Osteoarticular TB	**2HRZE**	**10HR**

[a] The standard code for TB treatment regimens uses an abbreviation for each medicine: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E). The number at the front of each phase represents the duration of that phase in months. For example, 2HRZE consists of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months.

[b] This includes all forms of EPTB except peripheral lymph node TB, TBM and osteoarticular TB.

[c] This includes all forms of TB involving the CNS.

Table 36*: Weight band table using widely available dispersible FDC*

		Duration in Months	Weight Band (Kg)/ Number of Tablets						
			Less than 2 kg	2-2.9	3-3.9	4-7.9	8-11.9	12 -15.9	16 - 24.9
Intensive Phase	HRZ (50/ 75/ 150)	2	1/4	1/2	¾	1	2	3	4
	E 100	2	1/4	1/2	¾	1	2	3	4
Continuation Phase daily	HR (50/ 75)	4	1/4	1/2	¾	1	2	3	4

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

Chapter 7

TB and Co-morbidities

7. TB and Comorbidities

Several medical conditions like HIV, diabetes, malnutrition, tobacco-smoking and alcohol-use are risk factors for TB and for poor TB treatment results. Therefore, it is important to identify these comorbidities in people diagnosed with TB in order to ensure early diagnosis and improve co-management. When these conditions are highly prevalent in the general population, they can be important contributors to the TB burden. Consequently, reducing the prevalence of these conditions can help prevent TB

7.1 Risk Factors and Comorbidities

Key risk factors and comorbidities such as HIV infection, diabetes, malnutrition, tobacco and substance use disorders drive the global TB epidemic and are associated with poorer TB treatment outcomes. People with TB also have a higher risk of mental health disorders. Conversely, TB and its treatment can complicate the management of some of these conditions. Collaborative TB/HIV activities and management of comorbidities is a key component of WHO's End TB Strategy.

- **People living with HIV** are 18-29 times (26–31) more likely to develop tuberculosis (TB) disease compared with people without HIV and living in the same country. TB is a leading cause of hospitalization and death among adults and children living with HIV, accounting for one in five HIV-related deaths globally. Integration of HIV and tuberculosis services reduced the annual number of people dying from HIV-associated TB globally from over 500,000 (2000) to 300,000 (2017) – a 40% decline.
- **People with undernutrition** increase the risk of tuberculosis (TB) and in turn TB can lead to malnutrition. Undernutrition is therefore highly prevalent among people with TB. It has been demonstrated that undernutrition is a risk factor for progression from TB infection to active TB disease and that undernutrition at the time of diagnosis of active TB is a predictor of increased risk of death and TB relapse. reviewed.
- **Tobacco Smokers** are almost twice as likely to be infected with TB and progress to active disease. Smoking interferes with TB at every stage of the disease. Secondly, it increases the risk of latent TB infection, culture conversion, sputum smear positivity, cavitary disease, treatment delay, treatment default, poor treatment outcomes and transmission of the disease. Some of these effects are mediated by a higher bacillary load among smokers. Thirdly, smokers are also twice as likely to die from TB.
- **Diabetes** triples the risk of TB. The association between diabetes and TB has been known for many years but studies in the last 10–15 years have highlighted that diabetes increases the risk of active TB and that patients with dual disease have worse TB treatment outcomes compared with those who have just TB alone. Strategies are needed to ensure that optimal care is provided to patients with both diseases. Diabetes prevalence is increasing globally due to socio-economic and lifestyle factors. Further increase in the number of diabetes-associated TB cases risks jeopardizing progress that has been made in the global fight against TB. Therefore, it is essential to have cross-screening, all adult TB patients should be screened for diabetes and all diabetes patients should be offered systematic screening for TB in high TB burden countries.

- **Disorders due to alcohol** use triple the risk of TB disease and who consume alcohol are twice as likely to have a poor TB treatment outcome (treatment failure, death, or loss to follow-up).
- **Mental health conditions** are common among people with TB, 45% of people with any form of TB have depression. There is an increased risk of depression, anxiety and psychosis among people with MDR-TB. TB and mental disorders together can lead to greater morbidity and poorer TB treatment outcomes.
- **Viral Hepatitis** and TB mostly coexists among PWID. PWID who have TB, two in three also have viral hepatitis, compared to one in three for HIV. Drug-induced liver injury is up to six times higher among persons coinfected with HBV or HCV who are receiving anti-TB drugs, and mortality rates are also higher during TB treatment among people with HCV.

Other health-related risk factors and comorbidities

- **Chronic respiratory disease** includes silicosis, asthma, chronic obstructive pulmonary disease, and lung cancer. Silicosis increases the risk of developing TB fourfold. WHO recommends TB screening among workers currently or previously exposed to silica, and people with silicosis are eligible for TB preventive treatment.
- **The COVID-19 pandemic** has caused a reduction in TB disease notifications worldwide due to disruptions in TB services. WHO has recommended measures to maintain essential TB services during the pandemic. People with COVID-19 who have TB are at a higher risk of mortality, as are those with HIV and HIV-associated TB.
- **People with disorders due to drug use (injecting and non-injecting)** have an increased risk of both TB infection and TB disease, irrespective of their HIV status. Drug use disorders are also associated with comorbidities such as HIV, viral hepatitis and mental disorders.

7.2 Interventions to address comorbidities

1. Reduce the burden of TB among people with health-related risk factors and comorbidities

- Find and treat TB among people with key health-related risk factors for TB disease, through screening or intensified case-finding, diagnosis and appropriate treatment.
- Prevent TB among people with identified health-related risk factors through the provision of TB preventive treatment and infection prevention and control.

2. Reduce the burden of comorbidities among people with TB

- Find and treat comorbidities among people with TB through screening, diagnosis and treatment of comorbidities associated with poor TB treatment outcomes.
- Prevent comorbidities among people with TB

7.3 TB/HIV Co-infection

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. People living with HIV are 18 times more at risk of getting TB than other populations.

7.3.1. Three I's Strategy

HIV care settings should also implement the WHO Three I's strategy:

- Intensified TB case-finding
- Isoniazid Preventive Treatment, now called as TB Preventive Treatment
- Infection control at all clinical encounters.

7.3.2. Intensified TB case-finding

All adults and adolescents living with HIV at every encounter with health care provider should be

- Symptom screened using WHO-recommended 4-symptom screening (W4SS) including cough, fever, night sweats, weight loss.
- Chest X-ray preferably with CAD (CAD is recommended for PLHIV >15 years)
- If screen positive PLHIV should be investigated for TB diagnosis using mWRDs
    - If TB is diagnosed, TB treatment should be started.
    - PLHIV who do not have any of these symptoms and CXR is normal, have a very low probability of having active TB and may be eligible to receive TPT.
- If there is still high clinical suspicion of TB, the active disease should be ruled out, If TB disease is ruled out, consider starting preventive TB treatment.
- Children living with HIV should also be screened at each visit using the WS44 and contact history with a TB case. Evaluation of TB disease should be done through the Pakistan Pediatric Association (PPA)) scoring chart (in chapter 5).
- All adults and children screen positive (W4SS and/or abnormal chest Xray) should be tested using Xpert MTB/RIF-ultra rather than conventional microscopy, culture, and drug susceptibility testing (DST). Xpert MTB/RIF should also be used in preference to conventional microscopy and culture for testing.
- Cerebrospinal fluid specimens from patients suspected of having TB meningitis.
- Respiratory specimens other than sputum including Nasopharyngeal aspirates, gastric aspirates and stool in children under 10 years of age.
- Non-respiratory specimens (lymph nodes, pleural fluid and other tissues) from patients suspected of having extrapulmonary TB.
- however, care must be taken in interpreting negative results as negative results do not rule out TB.

7.3.3 Tuberculosis Preventive Therapy (TPT)

Previously single-agent (Isoniazid) was used for prevention and hence called Isoniazid Preventive Therapy. (IPT). Now with more options available for TB prevention, TPT is the term now used for preventive therapy. TPT reduces the risk of developing active TB in patients with HIV.

All people living with HIV should be screened for TB. All patients who screen negative for active TB should be offered TPT. Following regimen can be used

- Daily INH 300mg for 6 months (3H)
- Weekly rifapentine and isoniazid for 3 months (3HP)
- Daily rifapentine plus isoniazid for 1 month (1HP)

Table 37: *Simplified dosing of TB and cotrimoxazole prophylaxis for infants and children who are at least 4 weeks of age*

Drug	Strength of tablet or oral liquid (mg/5ml)	Number of tablets (or ml) by weight band(kg) once daily					
Weight Band (kg)		**3-5.9**	**6-9.9**	**10-13.9**	**14-19.9**	**20-24.9**	**25-34.9**
Co-trimoxazole	200/40 per 5 ml	2.5ml	5ml	5ml	10ml	10ml	
	400/80 per 5ml		2.5ml	2.5ml	5ml	5ml	
	100/20 (DT)	1	2	2	4	4	
	400/80 (Scored Tab)	-	0.5	0.5	1	1	2
	800/160 (Scored Tab)	-	-	-	0.5	0.5	1
TB Prophylaxis Regimens for Children							
Weight Band (kg)		**3-5.9**	**6-9.9**	**10-13.9**	**14-19.9**	**20-24.9**	**25-34.9**
B6	50mg	-	-	-	0.5	0.5	1
6H**	100mg	0.5	1	1.5	2	2.5	1
Weight Band (kg)		**4-7.9 kg**	**8-11.9 kg**	**12-15.9 kg**	**16-24.9 Kg**	**25-39.9 kg**	**40-54.9 kg**
3HR	75/50	1	2	3	4	5	3
Weight Band (kg)				**10-14kg**	**14.1-25kg**	**25.1-32kg**	**32.1-49.9kg**
3HP	Isoniazid (100mg) + Rifapentine (150mg)			(25mg/kg rounded) * (300mg) 2tab/week for 12wk	(25mg/kg rounded) * (450mg) 3tab/week for 12wk	(25mg/kg rounded) * (600mg) 4 tab/week for 12 weeks	(15mg/kg rounded) * (750mg) 5 tab/week for 12weeks
MAC Prophylaxis for Children							
Azithromycin 20mg/kg once weekly or Clarithromycin 7.5mg/kg given twice daily							

7.3.4. Infection control in clinical encounters

People living with HIV are at high risk of acquiring TB in health care facilities and congregate settings. Each health care facility should have a TB infection control plan for the facility that includes administrative, environmental, and personal protection measures to reduce the transmission of TB in health care and congregate settings and surveillance of TB disease among workers. PLHIV should be screened at every encounter and sample for testing should be collected on site (at ART centers) and transported for testing, rather than referring PLHIV to TB clinics OPD.

7.3.5 Principles of treatment of TB in HIV patients

Patients co-infected with HIV and TB should receive the standard anti-tuberculous regimens and ART as per protocol. While the treatment of TB in HIV follows the same principles as in a non-HIV-infected person, it should be noted that patients with TB/HIV co-infection should receive at least six months of a rifampicin-containing treatment regimen. Intermittent dosing is not recommended for HIV patients with TB, similar to HIV- negative TB people. The optimal dosing frequency is daily during the initial and continuation phases.

For children with HIV and TB, weight-appropriate dosages of ATT should be used (Isoniazid 10mg/kg, Rifampicin 15mg/kg, Pyrazinamide 30-35mg/kg, Ethambutol 20mg/kg).

Unique to HIV/TB co-infected patients are the drug-drug interactions and the optimal time to start ARVs. Briefly, care must be taken when rifampicin and ART are given together. ART should be started within 2-8 weeks of starting ATT. If the child is already stable and on an ART regimen & develops TB while on therapy, the regimen should be adjusted.

Table 38: TB and ART Initiation

Opportunistic infections	**ART initiation**
Tuberculosis	Within the first 2 weeks if CD4 count < 50/mm^3 Within the first 8 weeks if CD4 count > 50/mm^3
	TB meningitis: initiating ART 4-8 weeks after the start of TB treatment.

A key contraindicated drug combination is Rifampicin and Atazanavir/ritonavir. When people co-infected with TB and HIV are receiving boosted Atazanavir, Rifampicin may need to be substituted with Rifabutin. If Rifabutin is unavailable, LPV/r can be substituted for Atazanavir for the duration of TB treatment.

MDR-TB and HIV co-infection pose a unique challenge, as mortality is higher if treatment for HIV is not initiated promptly. However, drug-drug interactions are not thought to be of concern as rifampin is not used in the MDR regimen, and while the exact metabolic pathways of some second-line drugs are not clearly understood, it is believed most of these drugs will not have significant drug-drug interactions.

If TB and HIV are diagnosed simultaneously, then ATT should be started first, followed by ARVs within 8 weeks. In patients with a CD4 count of <50 cell/mm^3 or those with MDR-TB, ARV should be started within the first 2 weeks of starting ATT.

Table 39*: Timing of starting ART in patients with TB/HIV co-infection*

Criteria	CD4 Count	TB Treatment	Antiretroviral therapy
Non-MDR Pulmonary TB	>50 cell/mm^3	Start Immediately	Start within 2 to 8 weeks of starting ATT
Non-MDR Extra pulmonary TB (except CNS TB)	>50 cell/mm^3	Start Immediately	
Non-MDR Pulmonary TB	<50 cell/mm^3	Start Immediately	Start within 2 weeks of starting ATT
Non-MDR Extra pulmonary TB (except CNS TB)	<50 cell/mm^3	Start Immediately	
MDR pulmonary or extrapulmonary TB (except CNS TB)	Any	Start Immediately	
CNS TB (regardless of MDR status)	Any	Start Immediately	Start 4-8 weeks after starting ATT

7.4 Diabetes and TB

Diabetes is a common condition and it is estimated to account for more than 10% of global TB deaths among HIV-negative individuals. Hyperglycemia induces abnormalities in both the innate and adaptive immune response to *M. tuberculosis*, and diabetes increases the risk (twofold to fourfold) that TB infection will progress to disease; also, the response to treatment is often worse in those with diabetes.

Clinically, impairment in immunity, translates into an increased proportion of sputum smear positive patients, with more extensive pulmonary disease bilaterally, larger number of cavities and lymph node enlargement, and "atypical" findings of lower lobe lesions (especially in patients with poor glycemic control). Diabetes has a negative effect on the pharmacology of some anti-TB drugs (e.g. rifampicin), with higher risk of development of drug-resistance. People with diabetes also suffer an increased rate of failure and death, and a higher risk of relapse.

Implementation considerations

- Individuals with diabetes and TB should receive the same treatment regimen as those without diabetes. However, due to the increased vulnerability of people with diabetes, all aspects of TB treatment must be optimized for this group, including correctly prescribed treatment regimens, patient support and supervision, diabetes testing, improved glucose control, and clinical monitoring as per national guidelines.
- Although the drugs used to treat DS-TB are generally well tolerated and are unlikely to cause serious adverse events among people with diabetes, treatment monitoring is important to ensure rapid notification and prompt management of any side-effects that eventually appear.
- Management of these patients involves a multidisciplinary approach in view of the additional need to control diabetes and the potential need to adjust drug dosing.

- A national or subnational body supporting the management of people with difficult-to-treat TB (i.e. a consilium) may be of help in specific cases.
- Supporting adherence is an important management component when treating people with DS-TB and diabetes. Therefore, collaboration with partners in the community, including family members, care-givers, health care workers, and welfare workers is essential.
- Coordination with diabetes services.

Metformin is not metabolized by the P450 enzyme system; its hypoglycemic effect may be increased by rifampicin, enhancing the expression of the organic cation transporter and the hepatic uptake of metformin. Insulin is not metabolized, no pharmacokinetic interactions with anti-TB drugs occur; therefore, it is recommended that it be used at the beginning of TB treatment, to achieve faster bacteriological sputum conversion and prevent drug–drug interactions.

7.5 Malnourishment and TB

Nutrition assessment and counselling

All individuals with active TB should receive (i) an assessment of their nutritional status and (ii) appropriate counselling based on their nutritional status at diagnosis and throughout treatment (strong recommendation, no evidence).

Management of Active TB with severe acute and moderate malnutrition:

In Table 37 below, WHO guidance for the management of Active TB with malnutrition.

7.5.1 Micronutrient supplementation

- A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition, but are unavailable (conditional recommendation, very low-quality evidence).
- All pregnant women with active TB should receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation, to complement their maternal micronutrient needs (conditional recommendation, very low-quality evidence).
- For pregnant women with active TB in settings where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of pre-eclampsia, particularly among those pregnant women at higher risk of developing hypertension, in accordance with WHO recommendations (strong recommendation, moderate quality evidence).
- All lactating women with active TB should be provided with iron and folic acid and other vitamin and minerals, according to the United Nations Multiple Micronutrient Preparation, to complement their maternal micronutrient needs (conditional recommendation, very low-quality evidence).

Table 40*: Management of Active TB in Malnutrition*

Active TB and severe acute malnutrition		
1	Children and adolescents, and adults, including pregnant and lactating women	Should be treated in accordance with the WHO recommendations for the management of severe acute malnutrition
Active TB and moderate undernutrition		
1	School-age children and adolescents (5 to 19 years), and adults, including lactating women, who fail to regain normal BMI after two months' TB treatment, as well as those who are losing weight during TB treatment, should be evaluated for adherence and comorbid conditions	They should also receive nutrition assessment and counselling, and, if indicated, be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status
2	Children who are less than 5 years of age	Should be managed as any other children with moderate undernutrition. This includes provision of locally available nutrient-rich or fortified supplementary foods, in order to restore appropriate weight-for-height
3	Pregnant women with active TB and moderate undernutrition, or with inadequate weight gain	should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to achieve an average weekly minimum weight gain of approximately 300 g in the second and third trimesters
4	Patients with active MDR-TB and moderate undernutrition	should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status

Contact investigation: In settings where contact tracing is implemented, household contacts of people with active TB should have a nutrition screening and assessment as part of contact investigation. If malnutrition is identified, it should be managed according to WHO recommendations (conditional recommendation, very low-quality evidence).

7.6 Chronic liver disease and TB

Patients with pre-existing liver disease require special consideration during TB treatment, particularly regarding the detection and management of hepatitis induced by anti-TB drugs including Isoniazid, rifampicin or pyrazinamide.

For the management of TB in patients with chronic liver disease (CLD), experts recommend monitoring aminotransferases (i.e. alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) on a weekly basis initially, and fortnightly after the second month of treatment, the TB treatment should immediately be withdrawn in cases where aminotransferase are

- Five or more times higher than the upper limit of normal (with or without symptoms), or
- Three or more times higher in the presence of symptoms or jaundice (i.e. bilirubin >3 mg/dL^{-1})

The responsible drugs should be identified, and a sequential reintroduction implemented once enzyme levels have returned to normal. The drug reintroduction should be performed one drug at a time, starting with the drug considered to be the least hepatotoxic, as follows:

- When aminotransferases return to less than two times the upper limit of normal, rifampicin may be restarted with ethambutol.
- After 3–7 days, after checking aminotransferases, isoniazid may be reintroduced, with subsequent rechecking of liver enzymes.
- If symptoms recur or aminotransferases increase again, the last drug added should be stopped and replaced with another from the list of the recommended drugs.

The severity of the chronic liver disease determines the use of hepatotoxic drugs; the more severe the liver disease, the fewer hepatotoxic drugs should be used. Pyrazinamide should not be given to patients with chronic liver disease. The following possible regimens may be given according to the severity of the liver disease:
Two hepatotoxic drugs are included in the treatment regimen (rather than the three in the standard regimen)
○ 9 months of isoniazid and rifampicin, plus ethambutol in the 2 months of initial phase;
○ 2 months of isoniazid, rifampicin, and ethambutol, followed by 6 months of isoniazid and rifampicin.
One hepatotoxic drug is included in the treatment regimen:
○ 2 months of isoniazid, ethambutol and followed by 10 months of isoniazid and ethambutol.
No hepatotoxic drug is included in the treatment regimen:
○ 18–24 months of ethambutol and fluoroquinolone.

If the clinical pattern indicates cholestasis, rifampicin may be the responsible drug. If the patient has prolonged or severe hepatotoxicity but tolerates isoniazid and rifampicin, a re-challenge with pyrazinamide may be hazardous. In this situation, pyrazinamide may be permanently discontinued, with treatment eventually extended to 9 months. In patients with advanced CLD, coagulation factors should be carefully monitored.

The Child–Turcotte–Pugh (CTP) score is based on albumin, bilirubin, prothrombin time/international normalized ratio (PT/INR), ascites and encephalopathy. The CTP score can be used as a predictor of tolerance to anti-TB drugs and the treatment outcome.

Implementation consideration

- TB program should consider stocking an extra supply of drugs to modify the HRZE regimen in the treatment of special situations such as CLD. Among the drugs that can be considered safe to use in patients with CLD are ethambutol and fluoroquinolones. Given their important bactericidal and sterilizing action, isoniazid or rifampicin (or both) should be included where possible.
- A patient's N-acetyltransferase (NAT) status affects their risk profile. Slow acetylators have a higher possibility of liver injury, so an isoniazid dose of 2.5–5 mg/kg/day may be adequate in such patients; in rapid acetylators, in contrast, the isoniazid dose may be increased to 7.5 mg/kg/day.
- In people with DS-TB and CLD, evaluation of the degree of impairment of the liver function is necessary, to design the best possible regimen that is sufficiently effective while not being aggressive for the liver. Given the clinical severity of these patients, collaboration with clinicians who have specific experience in CLD and the support of an expert committee (e.g. TB consilium) is recommended.
- The NTP should ensure a stock of individual formulations to manage patients with CLD who are unable to tolerate the standard recommended regimens.
- Treatment outcomes are often less favorable in patients with CLD than in patients without CLD.

7.7 Chronic renal failure and TB

Patients with chronic renal failure (CRF) have more frequent adverse events and higher mortality rates than patients without CRF. This has been attributed to increased host susceptibility from the cellular immunosuppressive effects of CRF and to social determinants of health among those with CRF.

The severity of renal insufficiency is classified using creatinine clearance: it is

- mild when the rate of clearance is 60–120 mL/minute
- moderate at 30–59 mL/minute
- severe at 10–29 mL/minute
- very severe at below 10 mL/minute

Creatinine clearance is calculated using the following formula:

body weight (kg) × (140 minus age in years) × 0.85 (in women) / 72 × creatinine value

1. Dose adjustments in adults with creatinine clearance below 30 mL/minute are as follows (unless otherwise indicated):
Pyrazinamide: 25–35 mg/kg per dose, three times per week after dialysis
Ethambutol: 15–25 mg/kg per dose, three times per week after dialysis
Rifapentine and moxifloxacin, which are both used in regimens for DS-TB, do not require renal dose adjustment.

- According to some experts, for patients with DS-TB on dialysis, thrice-weekly dosing of pyrazinamide and ethambutol should be administered after the dialysis cycle.
- Experts recommend close monitoring of creatinine every week or every 2 weeks, and adequate hydration. Given the frequent occurrence of electrolyte disturbances in CRF, weekly monitoring of electrolytes is also recommended.
- In the case of severe hypokalemia, treatment is with intravenous potassium chloride (KCl) at 10 mEq/ $hour^{-1}$ (10 mEq of KCl will raise the serum potassium by 0.1 mEq/L^{-1}). If the potassium level is low, checking the magnesium is recommended by experts; if this is not possible, empirical treatment with magnesium (i.e. magnesium gluconate at 1000 mg twice daily) should be considered in all cases of hypokalemia. The use of spironolactone, 25 mg daily, is suggested in refractory cases.
- Given the risk of QT prolongation (particularly due to moxifloxacin) and electrolyte imbalance, an ECG should be performed, considering that hypokalemia may be refractory if the concurrent hypomagnesemia is not corrected; the risk is higher if the intensive phase of treatment is prolonged for any reason; and electrolyte disturbances are reversible, although the disturbance might last weeks or months.

Implementation considerations

- Both the diagnosis of CRF and the treatment of TB in patients with CRF are challenging. There is little evidence to support evidence-based guidance for these patients.
- Given the complexities of the management of TB disease in patients with CRF, a close collaboration between infectious disease specialists, pulmonologists and nephrologists in this patient population is necessary. A TB Consilium (body of advisors) to support the management of people with TB that is difficult to treat may be considered as well.

7.8 Mental health conditions and substance use disorders:

Background and rationale

Mental disorders[1] are prevalent in all countries (8). Nearly 1 billion people worldwide are living with a mental disorder, which has become the leading cause of years of living with disability. The risk factors for developing a mental disorder are multi-faceted and may include any combination of individual factors (psychological or biological), family or community factors (such as poverty or violence), and structural factors (such as inequality or environmental emergencies).

People affected by TB have a higher risk for mental health conditions and substance use disorders. This comorbidity negatively impacts a person's capacity to adhere to their medication and infection control practices. It can also worsen morbidity and increase risk of poor TB treatment outcomes and poor overall health-related quality of life.

Several of the anti-TB medications are associated with depression, anxiety and/or psychoses, which may require either temporary or complete suspension of the suspected agent and/or initiation of adjunct psychopharmacological medication.

There is an increased risk of depression, anxiety or psychoses in people with multidrug resistant TB (MDR-TB). Psychological stress associated with stigma and discrimination may also trigger or aggravate mental health conditions in affected individuals. Individuals with drug-resistant TB and/or co-infected with HIV are at an even higher risk for mental health conditions.

However, the availability of services for mental health and substance use are largely inadequate in Pakistan. For this reason, opportunistic identification may be a prudent use of existing resources: health workers can initiate identification when a person accessing TB care appears with signs of the common presentations of mental disorders. Identification can be achieved through use of screening tools for mental health and substance use.

7.9 Epilepsy

Every TB patient with epilepsy should receive treatment for TB; however, the anti-epileptics have drug interaction with Rifampicin and Isoniazid. Their plasma levels are deranged while taking Rifampicin and Isoniazid, so the dose of the anti-convulsant should be adjusted(increased), and the patient should be monitored closely for increasing seizure frequency

Chapter 8

Drug-Resistant-TB (DRTB)

8. Drug Resistant TB

Pakistan ranks fifth among the 20 high RR/MDR-TB burden countries. According to Global TB Report 2023, there was an estimated 15000 MDR/RR-TB cases in 2022, with an incidence rate of 6.2 per 100,000 population. The prevalence of drug-resistant TB cases is estimated at 2.3% in new cases and 4.6% in previously treated TB patients.

8.1. Commonly used terms and key definitions in DR-TB treatment

Bacteriologically confirmed: when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for TB as recommended by WHO.
Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is **resistant to any TB medicines.**
Rifampicin-susceptible, isoniazid-resistant TB (HR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is **resistant to isoniazid but susceptible to rifampicin.**
Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is **resistant to rifampicin**. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines.
Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is **resistant to both, Rifampicin and Isoniazid.**
MDR/RR-TB: refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).
Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is **resistant to rifampicin** (and may also be resistant to isoniazid), and that is **also resistant to at least one fluoroquinolone** (either levofloxacin or moxifloxacin).
Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is **resistant to rifampicin** (and may also be resistant to isoniazid), and that is **also resistant to at least one fluoroquinolone** (levofloxacin or moxifloxacin) **and to at least one other "Group A" drug** (bedaquiline or linezolid).
Extensive (or advanced) pulmonary TB disease: the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.
Severe extrapulmonary TB: presence of Milliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) is considered severe
Serious adverse event: an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly (detected at birth or at a later stage). Adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

8.2 Mechanism of drug resistance and Factors Contributing to DRTB

Members of the genus Mycobacterium have long been noted for their intrinsic resistance to a wide array of antibiotics. The majority of drug resistance in clinical *M. tuberculosis strains* is attributed to chromosomal mutations in existing genes that are passed along from mother to daughter cells through vertical descent. TB bacilli spontaneously mutate, but resistance develops if TB drugs impose selection pressure on MTB populations, reducing drug-susceptible bacilli, the advantageous reproduction of drug-resistant mutants, and the emergence of drug resistance.

The primary vehicle driving drug resistance in MTB is the acquisition of mutations in genes that code for drug targets or drug-activating enzymes. By 1998, resistance-conferring mutations were discovered for classical first and second-line TB drugs including H (alterations in genes *katG* and *inhA*); R (in *rpoB*); streptomycin (in *rrs* and *rpsL*); Z (in *pncA*); ethambutol (in *embB*); FQ (in *gyrA*); and kanamycin (in rrs). However, the targeted amplification and sequencing of known or suspected resistance genes revealed that these mechanisms were insufficient to explain all phenotypic resistance. Resistance mechanisms for several newer drugs including Bedaquiline, Delamanid, and Pretomanid were discovered during a period when whole genome sequencing (WGS) was becoming routine.

Resistance could be present either at the onset of the disease as a result of the transmission of drug-resistant strains (primary drug resistance] or might emerge during the course of the disease due to inadequate treatment (acquired drug resistance).

Various risk factors identified associated with the emergence of drug-resistant TB include previous TB treatment, poor adherence to treatment regimens, inadequate regimens, sub-optimal dosage and poor drug quality.

8.3 DRTB Management

Early TB diagnosis, detection of drug resistance, precise treatment prescription by well-trained health care providers, comprehensive social support for the duration of the treatment and infection control measures are some of the critical elements of the DRTB management. All treatment offered to people with MDR/RR-TB should align with WHO-recommended standards, including

- Access to DST
- Patient-centered care and support
- Informed consent where necessary
- Principles of good clinical practice
- Active TB drug safety monitoring and management (aDSM)
- Regular patient monitoring to assess regimen effectiveness
  - clinical and bacteriological follow-up to assess the TB treatment response
  - general laboratory support to monitor and manage adverse events and comorbidities
- The provision of social support is essential to enable adherence to treatment

Certain programmatic components (e.g. aDSM) are recommended for all patients on any MDR/RR-TB regimen. An appropriate schedule of laboratory tests and clinical examinations should be included in the patient's treatment chart to identify adverse events.

8.3.1 Access to Drug Susceptibility Testing (DST)

The current guidelines for treatment of DR-TB stress the need for access to reliable, quality-assured DST, to inform on the use of the WHO-recommended regimens. Rapid molecular testing has made it increasingly feasible to detect MDR/RR-TB and other types of resistance quickly, and to use the results to guide treatment decisions. Rapid molecular testing is increasingly being made available and accessible in the country, to ensure DST for at least rifampicin, isoniazid and fluoroquinolones, given that DST for these drugs is essential for selecting the most appropriate initial DR-TB regimen.

No rapid molecular testing is currently available for ethambutol, Bedaquiline, Clofazimine, Linezolid, Pretomanid and Delamanid. National and provincial programs are working towards the establishment of phenotypic DST for all TB medicines for which there are now agreed reliable and reproducible methods (e.g. Bedaquiline, Clofazimine, Delamanid, Fluoroquinolones, Isoniazid, Linezolid and Rifampicin). It is important that clinical specimen is processed for culture at the start of treatment and DST be performed for new drugs. Culture-based DST for fluoroquinolones is also important, especially in the high prevalence of resistance to these drugs in Pakistan.

WHO has recently recommended the use of targeted next generation sequencing (tNGS)solutions, which may provide an opportunity for rapid molecular testing for multiple anti-TB drugs.

8.3.2 Regimen options in the treatment of DR-TB

TB medicines for DRTB are classified in three groups (A, B and C) as per the below table. The rankings are determined by considering the balance between effectiveness and safety.

Table 41: *Grouping of medicines recommended for DR-TB regimen*

Group	Medicine	Abbreviation
Group A Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx , Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin OR Meropenem	Ipm-Cln, Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide OR Prothionamide	Eto, Pto
	p-aminosalicylic acid	PAS

For patients with MDR/RR-TB, WHO recommendation has recommended several regimens. The key factors that define treatment regimen choice include drug-resistance profile, prior exposure to TB medicines and patient history, drug-resistance profile of close contacts, the patient's age, extent of pulmonary TB disease and localization of extrapulmonary TB lesions.

- **BPaLM regimen (6 Bdq-Pa-Lzd-Mfx[1])**: in patients with MDR/RR-TB where fluoroquinolone susceptibility is presumed or documented. This 6-month all-oral treatment regimen comprises **B**edaquiline, **P**retomanid, **L**inezolid and **M**oxifloxacin. It is possible to omit moxifloxacin and continue with the BPaL regimen for MDR/RR-TB patients with confirmed Fluoroquinolone resistance.
- **9-month all-oral regimen (4–6 $Bdq_{(6\,m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto or $Lzd_{(2\,m)}$ / 5 Lfx/Mfx- Cfz-Z-E)**: in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. The 9-month all-oral regimen comprises Bedaquiline (used for 6 months), in combination with Levofloxacin/Moxifloxacin, Ethionamide, Ethambutol, Isoniazid (high dose), Pyrazinamide and Clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by treatment with Levofloxacin/Moxifloxacin, Clofazimine, Ethambutol and Pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of Linezolid (mSTR).
- **Longer individualized regimens**: for patients with MDR/RR-TB who are not eligible for or had no favorable treatment outcome using the above 6-month or 9-month regimens, have TB disease caused by M. tuberculosis strains with extensive drug resistance (e.g. extensively drug-resistant TB [XDR-TB]) or have an intolerance to key components of the above-mentioned regimens. These regimens have a duration of at least 18 months and are individually designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history.

Table 42: Regimen options and factors to be considered for selection of treatment regimen for patients with MDR/RR-TB

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.

Pretomanid (New drug): It is part of B PaL/M regimen and cannot be prescribed separately or in any other combination so far.

Based on the review of the latest available evidence, the 6-month BPaL-M regimen is the preferred option for most patients with MDR/RR TB

8.4 *Follow-up of DRTB patients:*

8.4.1. Monitoring treatment response:

Treatment progress is tracked clinically by assessment of improvement in general condition, symptoms, weight gain. Simultaneously treatment response is monitored by bacteriology through monthly sputum microscopy and culture. The combined use of microscopy and culture helps in identifying patients whose sputum remains positive or reverts to positive after initial conversion indicating delayed or failure to respond to treatment. The regular monitoring of treatment response can assist clinicians in identifying patients whose treatment is likely to fail, allowing them to plan alternative options and implement infection control measures promptly. DST is also recommended for detection of emergence of additional drug resistance.

8.4.2. Monitoring for adverse events:

Given the increased use of newer and repurposed medicines in combination MDR-TB regimens, aDSM is particularly important. aDSM defines the active and systematic clinical and laboratory assessment of patients on MDR-TB treatment to detect, manage and report suspected or confirmed drug toxicities. It applies the principles of active pharmacovigilance to the specific needs and context of NTPs and is embedded within the routine patient monitoring function (e.g. treatment outcome cohort monitoring) of NTPs. The selected medicine in the treatment regimen determines the need of a monitoring schedule including clinical assessment and laboratory tests. Few examples are given in Table 43.

Table 43: *DRTB Drugs and Monitoring Adverse Drug Reactions*

Drug in regimen	Monitoring
INH(HD), Cycloserine, Linezolid and Ethambutol	Clinical assessments to identify optic and peripheral neuropathy and psychiatric disturbances
Linezolid especially when used for a longer period	Clinical and biochemical assessments to identify pancytopenia, lactic acidosis and peripheral neuritis including frequent eye or visual assessment and any potential drug–drug interaction (e.g. serotoninergic syndrome)
Bedaquiline, Delamanid, Moxifloxacin and Clofazimine	ECG and monitoring of electrolytes, particularly when the regimen contains multiple QT interval prolonging agents – in the case of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed

8.4.3. Psychosocial Support for DRTB Patients:

Social support is very important to a people-centered approach to improve the well-being of people infected with TB and to support treatment plans by addressing the barriers described above. Social support must be available for people throughout TB treatment, from diagnosis to the conclusion of the treatment.

Social support should be made up of four resources, namely:

1. Informational support is information or education that helps a person to solve problems and reduce stress; it includes training and education on the medications a person is taking, their possible side effects, how treatment is monitored, and how the success of treatment is determined.
2. Psychological (emotional) support refers to all types of care that strengthen self-esteem through understanding, trust, encouragement and care, and that help to deal with the psychological challenges in life.
3. Material support includes financial support which could be money (e.g. grants from the government), food support, travel support or anything that helps the patient with the financial costs of TB disease and its treatment.
4. Companionship support is help that makes a person feel that he or she belongs to the social system and that he or she can rely on it for certain needs.

Chapter 9

TB Case Management in Public Private Mix (PPM) and Other Settings

9. TB Case Management in Public Private Mix (PPM) and Other Settings

9.1. Engaging All Health-care Providers in TB Control

In Pakistan, over 80% of patients with various ailments, including TB symptoms, seek care from private healthcare providers. These providers include for-profit and nonprofit entities and other public sector institutions. Many of these providers do not report TB cases to the NTP, and the quality of TB services and treatment outcomes in this sector is largely unknown.

The public sector provides almost full coverage for TB care, but only a small portion of the private sector is involved with NTP reporting. Engaging all health care providers in TB control is crucial for the WHO Stop TB strategy and the new END TB Strategy and National Strategic Plan for Tuberculosis. The involvement of health care providers outside the TB program network is a key component of Pakistan's national strategy for TB prevention, care, and control. The TB Program has extensive experience in implementing the PPM approach which was initiated in 2005. **In 2023, 41% of TB cases reported in Pakistan were notified through the private sector**. The NTP/PTPs is in the process of consolidating and scaling up TB activities through several innovative approaches, including engaging all care providers.

9.1.1. Guiding Principles for Public Private Mix (PPM) Approaches in TB Control

The following principles are recommended for public-private partnerships:

- The National Policy for Mandatory TB case Notification applies to all health care (Public& Private) providers.
- Recommended Diagnostic & treatment protocols shall be adopted by Private providers
- TB Programs shall provide ATT and TB lab diagnostic supplies as per requirement, through its existing supply mechanism.
- Private partners shall be given access to diagnostic services in public sector if not available in private sector. However, the services availed should be acknowledged and TB patients diagnosed shall be notified.
- Standard recording and reporting tools either in paper or electronic forms shall be used and may be adapted by private sector context.
- Provincial and district health authorities, along with partners, shall be responsible for the overall supervision and monitoring of all TB control activities in the private sector.
- Context-specific M&E tools shall be used. NTP encourages mobile applications and other innovative technologies for monitoring & surveillance.
- Performance based Incentives with good rationale may be provided only if considered unavoidable. This should be done subject to availability of resources in consultation with stakeholders.
- Standardized training protocols are recommended; however, specific training modules, and methodology may be contextualized based on private sector demand and limitations.

9.1.2. The PPM Models in Pakistan

TB Program developed 5 models under the Public-Private Partnership (PPP):

- **PPM 1** which focuses on engaging private GPs: In this model the solo GPs, specialists and clinical laboratories in private sector are engaged. All TB related activities are implemented under the stewardship of the district health department. The intermediary body is an NGO, mainly responsible for coordination between the private health care providers and the public sector, the provision of logistics, and the organization of community awareness activities.
- **PPM 2** which targets health facilities of NGOs. In this model different "network of non-government organizations providing health care" are engaged.
- **PPM 3** which deals with private hospitals. In this model private hospitals including large tertiary Care Hospitals e.g. (Gulab Devi, AKU and Indus Hospital) are engaged.
- **PPM 4** which considers parastatal hospitals. This includes other public sector organizations that are not under the Department of Health and have their own health care system for employees and families, i.e., Army, Social Security, Fauji Foundation, WAPDA, Railways Cantonment Board, etc.
- **PPM 5** focuses on private pharmacies. The pharmacists in these either refer presumptive TB cases or patients who demand TB medication over the counter prescribed by a doctor that is not in the NTP network, which may be public or private.

In all these models, technical support, including training, drugs and diagnostics, recording and reporting tools, is provided by the Provincial TB Control Program through the district TB program. TB cases are notified to the district notification system.

9.2. Hospital TB Linkages

The health system of Pakistan comprises of three tiers primary, secondary & tertiary care (TCH's). The significantly higher proportion of TB patients approach secondary & Tertiary Care Hospitals and these hospitals currently register more than 50% of the total National TB notification.

A large number of TB patients are at risk of being missed because cases are scattered across hospitals, and there are ineffective linkages between different departments. There is no centralized reporting system for TB cases, and patients traveling long distances to hospitals are more likely to be lost to follow-up if not properly referred to nearby facilities for treatment.

An effective "***external network***" will ensure that enrolled patients successfully complete their treatment. An updated directory of the health care facilities offering TB care services within each district /province shall be available with the coordinator. The importance of treatment compliance shall be discussed with the patient, and referral shall be offered to patients coming from a distance according to their home address or any other preferences. Patients shall be referred with a referral form, and the referring site shall be contacted for feedback.

Since the ***external network*** depends on a functioning linkage between the TCH and peripheral health care facilities, the same shall be utilized for retrieving lost-to-follow-up (LFU) cases.

The key hospital TB services staff shall have invited for participation in intra district meetings organized by the district TB Control program. Interaction with staff working in other health care facilities within same district will help in strengthening linkages.

9.3. TB Care in Prisons and Congregate Settings

Prison is a term used for any place of detention. It includes centers for pre-trial convicted prisoners as well as centers for juvenile offenders and illegal immigrants. Pakistani facilities are classified as central prisons, special prisons, district prisons, and sub-jails Number of establishments / institutions are 116 with Official capacity of 64,099 of prison system. With occupancy level of 136% based on official capacity (World prison Brief 2022)

Prisoners do not represent a homogenous segment of society. Many are poorly educated and come from socioeconomically disadvantaged groups. They are usually young (15–44 years) and are exposed to unhealthy habits or addictions, such as alcoholism, smoking, and drug use, which contribute to their poor health and vulnerability to developing various diseases including TB. Due to risky behaviors the prisoners may enter the prison already ill or may acquire illness in the prison as they are exposed to higher risk of becoming ill compared to the general population3. Furthermore, Prisons are usually overcrowded with low standards of hygiene and low quality of health care that promote illness and transmission of infection to other prisoners and sometimes the prison staff. The number of MDR-TB cases in prisons is often proportionally higher than that found in the general population of a given country.

Key Recommendations

- A systematic approach is recommended to introduce a TB Control Program in Prisons and other congregate settings which includes:
    - All infectious diseases including TB should be given a priority in overall health management in prisons and other congregate setting as the inhabitants act as a reservoir for TB, spreading the disease into the civilian community through staff, visitors and inadequately treated former inmates.
    - Prisoners should be provided access to quality TB care as part of the basic human right.
    - TB control program in prisons should be implemented within a formal policy framework with relevant departments.
    - Develop an Operational Plan for the collaboration for TB control in prisons with terms of reference.
    - Conduct a baseline assessment of TB situation (epidemiology) and control practices in prisons.
    - Establish the diagnostic and treatment facility for TB care integrated with existing health care system in prisons.
    - Establish surveillance system integrated with district and provincial TB Control Programs.
    - Advise/implement infection control measures based on baseline assessment.

- The objective of TB control efforts in congregate setting is early TB case detection and reduce the risk of TB transmission in and outside the congregate setting. TB care services shall be established for diagnoses and treatment of patients on routinely basis and will ensure:
    - Diagnosis of TB cases through entry screening as he enters prison.
    - Diagnosis in prisons who develop symptoms during their stay in prison.
    - Treatment monitoring through follow-up examination.

However, as risk of transmission is high, active case finding and mass screening is recommended for early detection.

Detecting TB through active case finding in Prisons

Symptoms screening shall be carried out at entry point of all prisons.

Any prisoner with a productive cough for more than two weeks shall be isolated in a single cell and assessed for TB as soon as possible.

TB symptomatic should preferably be tested using Xpert/MTB assay. However, if only microscopy services are available on site, sputum shall be referred for Xpert testing after making AFB smear. At minimum all AFB smear positive specimen should be referred for Rifampicin testing to Xpert site if transport services are not available for all specimens.

Mass screening in Prisons

Mass screening is useful in finding undetected TB cases e.g. at start of supervised TB treatment and also those who are asymptomatic (if X-ray are used in screening). Mass screening thus complements supervised TB treatment services but is not advised to replace routine services.

Contact Investigations

- In congregate and overcrowded settings such as prisons, contact investigation to detect TB Patients is crucial and should be prioritized and carried out in an active and prompt manner. Scope of contact tracing should be determined by the time of TB diagnosis in prisoner.
- During stay in prison: All prisoner who share the cell, prison staff that comes in contact with a TB case, & visitors should be investigated.
- At entry in prison: Contact investigation should also be extended to contacts before entry into the prison e.g. Households.

9.4. TB Care in Refugees and Displaced Population

Refugees and displaced populations are at particularly high risk of developing TB. The crowded living conditions of these populations can facilitate the transmission of TB infection. Coexistent illness, particularly HIV and poor nutritional status, can further weaken their immune system and make them more vulnerable to developing active TB. TB is an increasingly important cause of morbidity and mortality among refugee and displaced populations.

Afghanistan, Iran and Pakistan have established strong national TB programs which have to date successfully ensured appropriate TB prevention, care and control services to populations, including migrants, refugees, returnees and IDPs.

The **following principles** should be adopted to strengthen collaboration between countries to provide quality TB care to the target population

- Establish inter-county coordination mechanism/steering committee.
- The TB service provision shall be harmonized among the three countries.
- The segregated information on migrants, refugees, returnees and IDPs with TB should also be collected routinely and recorded within the NTP networks.
- Development of a multi-country TB database that will allow cross-country tracking of patients and evaluation of treatment outcomes.
- The country protocol shall be available in all treatment facilities engaged in cross border TB management.
- The recording and reporting as well as the monitoring and evaluation system shall also be incorporated.
- Strengthening of diagnostic services in refugee settings with provision of active case finding activities in refugee settings.
- Use of innovative technologies for treatment support and referrals.
- Targeted information and education activities in refugee, migrants and returnees' settings.
- Address removing human rights and gender related barriers to TB care and prevention.
- Prepare contingency plans in advance for episodes of insecurity, unexpected movement of the camp or population, and repatriation or transfers to another Program.
- The plan should also include the management of drug stocks in order to prevent TB drugs being taken and circulated freely in the community.

Chapter 10

TB Infection Prevention and Control

10.TB Infection Prevention and Control

Preventing tuberculosis (TB) infection and stopping progression from infection to disease are critical for reducing TB incidence to the levels envisaged by the End TB Strategy. The main health care interventions to achieve this reduction are TB preventive treatment (TPT), which the World Health Organization (WHO) recommends for people living with HIV, household contacts of people with TB and other risk groups. Strategies to provide TPT are often linked to screening to find and treat people with TB earlier in the course of their disease and thus help to reduce transmission and improve outcomes. Other TB preventive approaches are TB infection prevention and control (TB IPC) and vaccination of children with the Bacillus-Calmette-Guérin (BCG) vaccine. Addressing broader determinants that influence TB epidemics can also help to prevent TB infection and disease.

10.1 TB Infection Control

Rapid detection of pulmonary TB patients should be the priority for every health facility, so that patients can be treated in time, way before spreading the infection. Thus, fast detection of the most infectious cases and proper treatment are two of the most important ways to prevent TB transmission.

Bacteriologically positive pulmonary TB patients are the most infectious cases because they spray tubercle bacilli into the air whenever they cough or sneeze. Contacts of bacteriological positive cases may become infected when they breathe in tubercle bacilli. The longer bacteriologically positive PTB cases are present in the home and community before beginning treatment, the greater the chances that they will infect others.

TB primarily spreads through airborne particles, typically 1-5 μm in size, emitted by individuals with pulmonary or laryngeal TB. These particles can linger in the air for extended periods and easily disseminate via ventilation systems. Inadequate transmission precautions, coupled with environmental factors like confined spaces, poor ventilation, and improper specimen handling, contribute to rapid infection spread in health care settings and communities. Speaking loudly for 5 minutes generates a similar number of infectious particles as coughing. Aerosol-generating procedures and recirculated air are linked to TB transmission and outbreaks in health care facilities, as well as in confined environments like school buses, naval ships, classrooms, and correctional facilities. Addressing these factors is critical for mitigating TB transmission risks and preventing outbreaks across various settings.

Promptly identifying coughers (triage), isolating them from other patients to the extent possible, asking patients to cover their mouth and nose when coughing or sneezing (cough etiquettes), and promptly initiating treatment while minimizing the amount of time that patients are in the health facility are all ways to decrease the possibility of transmission of TB and other airborne infections in the facility.

Another way to prevent TB transmission is to bring fresh air into areas of the health facility where infectious TB patients and TB presumptive cases cough or sneeze while waiting, seeing a health

worker or walking from one area to another. Good ventilation dilutes and exchanges the room air with fresh air, thereby reducing the number of particles remaining in the air and reducing the risk of another person becoming infected with TB in the facility.

10.2 Principles of TB infection control in a health care facility

10.2.1 Managerial Control

Certain principal activities are required for implementation of TB infection control which are as follows:

- Identification of a coordinating (IPC) body and development of a comprehensive infection control plan that includes human resource requirements and procedures to ensure proper implementation of the administrative controls, environmental controls and use of particulate respirators. Nominate at least one Infection Prevention officer (doctor/nurse) per TB ward to monitor and improve the IPC Practices including Occupational safety.
- The health facility should have IPC committee to oversee all IPC practices. Conduct trainings and orientations of health care workers on IPC Plan for health facility (specially TB ward). IPC committee should review TB Infection Prevention & Control plan on an annual basis.
- Site risk assessment to ensure appropriate use of available spaces to optimize the implementation of infection control measures (risk assessment should be on annual basis).
- Surveillance of TB disease for health care workers. There should be an annual screening of health care workers working in TB unit (with one baseline two-step TST or one IGRA result in the start and pre-service screening) and interpret results as per the risk assessment.
- Provide occupational health services to health care workers of TB unit including screening, evaluation, leaves in case of exposure and positive TB, vaccination and proper Personal Protective Equipment.
- Advocacy, communication and social mobilization including engagement of civil society.
- Monitoring and evaluation of TB IC measures.
- Operational research.

10.2.2 Administrative control

Administrative controls act as a first priority because they have been shown to reduce transmission of TB in health-care facilities. Such controls are a vital part of sound infection control practices, which require people with TB symptoms to be promptly identified, separated and treated. Some of activities under administrative control are as under:

- Promptly identify people with TB symptoms (triage): People suspected of having TB must be separated from other patients & placed in well-ventilated areas (negative pressure ventilation). Isolation protocols should be adopted not only in the TB ward, but also in emergency department and OPD clinics of the TB where patients (suspected and confirmed) should be isolated by 6 feet with modified seating plan. All patient coming to TB clinic should have at least a mask and IEC material regarding appropriate transmission-based precautions including cough etiquette should be placed and implemented. Ideally there should be a

person in OPD and Emergency department to rapidly identify the suspected case of TB through proper interview form or simply asking few major questions (during patient slip generation or in waiting place).

- Cough etiquette and respiratory hygiene: In order to minimize the spread of infection patients, attendants and health care workers need to adhere to cough etiquette i.e. cover their nose and mouth when sneezing and or coughing. Physical barriers may include surgical masks that may also help spread of transmission. Proper waste management of masks and otter physical barriers should be done as per the protocols of highly infectious waste.
- Reduction of diagnostic delays.
- Prompt initiation of treatment.
- After isolating the patient, educate them and their family about infection prevention practices and risks of breaching transmission precautions. Even in isolation, the patient should cover their mouth when coughing and dispose of tissues properly. If the patient needs to leave the room, ensure they wear a surgical mask at all times. Discontinue isolation for confirmed patients after at least two weeks of appropriate treatment, good clinical response, and three consecutive negative AFB smears. This ensures comprehensive protection against transmission within health care settings

10.2.3 Environment (airborne) control

Adequate ventilation in health-care facilities is essential to prevent transmission of airborne infections. This can be achieved by air mixing and efficient cross ventilation in an enclosed area.

In a health facility emphasis is on primary environmental controls consist of controlling the source of infection by using local exhaust ventilation diluting and removing contaminated air by using general ventilation.

All rooms housing TB patients ideally must maintain negative pressure compared to hallways, with a recommended minimum of 6-12 air exchanges per hour. New facilities should ensure at least 12 exchanges per hour. Ventilation systems should expel air from TB units outside, away from facility ventilation intake. Split air conditioning systems with hallway exhaust units pose high infection spread risk. Centralized AC systems serving both TB units and other areas should cease. Instead, TB unit and outpatient clinic air handling units should be separate, not sharing centralized machinery with other areas. This separation is crucial as ventilation systems are a major, often undetected, source of TB spread in health care settings. Prioritizing these ventilation measures mitigates the risk of TB transmission, safeguarding both patients and health care workers. Secondary environmental controls may also be applicable where prevention of air contamination by using high efficiency particulate air (HEPA) filtration or UVGI can be achieved. In low resource setting where natural air mixing in simpler way is the only solution, make sure that the air entry and exhaust is from different sides and air removal (after dilution) is not directly in hallways or corridors (or nearby departments), and patients remain wearing surgical masks. The windows should not open in corridors, and it is only allowed in extreme low resource settings and areas where no procedure of aerosol generation is performed.

The doors of the patient rooms should be kept closed at all times to maintain proper negative pressure and airflow. All doors should have automated door closers (high efficiency or locally made). Bacteriologically positive TB patients admitted in other units should be shifted to Isolation units/TB wards, and health care workers should visit the patient fulfilling all TB isolation precautions. In choosing a ventilation system (i.e. natural or mechanical) for health care facilities, it is important to consider local conditions, such as building structure, climate, regulations, culture, cost and outdoor air quality. Positioning and placement of indoor furniture is also essential to avoid direct exposure to a coughing patient and also protect the health care worker from acquiring TB infection.

Elective surgeries should be postponed until patients are out of isolation. If not possible, take precautions to minimize infection spread. Operate as the last case, transitioning directly from isolation to the OR. Use antibacterial filters on tubes. Ideally, return to isolation before extubating; if not, extubate in the OR with HEPA filters. Keep doors closed, using a damp towel to prevent air movement. Doors remain shut until 99% of contamination is removed by ventilation (time calculated). These measures prioritize patient and staff safety during surgical procedures, reducing the risk of infection transmission in health care settings.

10.2.4. Use of personal protective equipment (PPE)

Masks are NOT a substitute for administrative or environmental controls. They can only improve personal protection when administrative & environmental controls are functioning optimally.

Health care workers may use particulate respirators (N-95) when caring for patients or those suspected of having infectious TB. Visitors who are not “TB contact” are also protected through N-95 while coming in contact with an infectious case, a fit test should be performed to ensure a tight facial seal before entering isolation rooms. Annual fit testing is highly encouraged. Strong behavioral change campaigns are to be preceded to avoid the stigma associated with its use.

In addition to complying with cough etiquette patients may also make use of surgical masks especially while visiting a health facility. This helps in reducing disease transmission mainly by reducing the spread of tuberculous bacilli in air while coughing, sneezing and talking. The surgical masks are not an alternative for N-95 and will not protect from contracting TB.

In particular, health workers should use particulate respirators:

- In areas with high risk of TB transmission (OPD, sputum collection areas, X-ray rooms, laboratory). There should be barrier precautions in OPD and Triage, such as glass barriers between patients and health care workers and infrastructure supporting occupational safety.
- In areas with high generation of aerosols bronchoscopy, intubation, sputum induction procedures, aspiration of respiratory secretions, and autopsy.

Table 44*: Patient pathway in the health facility*

Patient flow in a health facility	Infection control measures
Patient (cougher) arrives at a facility	Screen patients to identify persons with symptoms of TB disease. Provide face masks or tissues to persons with symptoms of TB disease and isolate to conduct further investigation
Prolonged waiting	Fast track TB suspects and cases to the front of the line to expedite their receipt of services (there should be separate hospital slip counter for TB patients)
Mixed with non-infectious patients	Segregate TB suspects and cases in a separate waiting area if available
Confined space	In case of a common waiting area, increase ventilation by: Opening of windows and doors where applicable Turning ON the ceiling and exhaust fans Rethinking regarding use of available space in a way that exposure to HCW is minimized. Make sure every patient wears surgical mask all the time he/she is in the room
Interaction with HCW during check up	Use of N-95 by HCW and surgical masks by patients/attendants in a high resource setting. Periodic surveillance for HCW to timely detect and manage TB. Training and education of HCW on infection control practices. In a low resource setting, HCW may interact with the patient in a well-ventilated open area with barrier between HCW and the patient (glass barrier, face screen etc.).
Sputum collection	Collection of sputum collection in a properly ventilated (negative pressured) area away from other population. (DO NOT COLLECT SPUTUM INDOORS). Wherever available collection of sputum in a designated area (sputum booth).
Monitoring & Evaluation	Continuous monitoring of the TB infection control practices to bring improvement as per need.

The effectiveness of these interventions relies on health care professionals promptly recognizing and isolating confirmed and suspected TB patients. Failure to do so endangers patients and health care workers. To mitigate this risk, it's crucial to initiate isolation precautions immediately for suspected TB patients, including negative-pressure room placement, N95 respirator use, and appropriate therapy continuation.

10.3 TB infection control in a household

Prompt and effective treatment stops TB transmission however, full compliance is a pre-requisite. Early case detection remains one of the most important interventions for reducing the risk of TB transmission in the household. Household members of persons with infectious TB are at high risk of becoming infected with TB and consequently developing the disease. The infection control messages need to promote the importance of early identification of cases, adherence to treatment and implementation of proper TB infection control measures (e.g. cough etiquette and respiratory hygiene) in the household, before and after diagnosis of TB. Community education and awareness campaigns may help in early detection and prevention of TB to households.

Family members of smear-positive TB patients may mitigate disease transmission risks by taking the following measures:

- Houses are to be adequately ventilated, particularly rooms where people with infectious TB spend considerable time (open windows and doors to aide natural ventilation wherever applicable).
- Anyone who coughs should be educated on cough etiquette and respiratory hygiene, while smear positive, TB patients should:
    - spend as much time as possible outdoors.
    - sleep alone in a separate, adequately ventilated room, if possible.
    - spend as little time as possible in congregate settings or in public transport (and having surgical mask on).
    - The handling of waste from the confirmed patient (masks, sputum, tissues etc.) should be done with precautions (wearing gloves if possible) and discard it as infectious waste and HCW should guide the patient and family regarding its importance. Proper hand hygiene (at least two seconds) with soup should be observed by the patient and the person caring the patient (before and after coming in contact with patient and/or belongings).
    - Patient family should be guided about the symptoms of TB and screening tests of family persons of the positive case (who has remained at home/close settings for longer periods with symptoms) should be conducted.
- Any health care provider while visiting a bacteriologically positive TB patient may observe the following measures:
    - Wear N-95 when attending patients especially in enclosed spaces. Preferably, attend the patient in an open ventilated area.
    - Ensure opening of doors and windows if applicable.
    - Verbal screen all contacts of a smear-positive patient and, if found presumptive, must be called to the health center to establish the diagnosis.
    - Children below five years of age are to be screened irrespective of presence of symptoms and if not found presumptive, are put on INH/ HR/ HP prophylaxis therapy (TPT).

10.4 Cleaning, Disinfection & Waste Management:

The contagious nature of symptomatic TB patients underscores the importance of meticulous waste management in various health care settings and communities. While transmission through surfaces is uncommon, reports highlight the potential spread via improperly disinfected instruments, such as bronchoscopes. Therefore, adherence to standard disinfection protocols and manufacturer instructions is crucial.

Janitorial staff cleaning isolation rooms must always wear N95 masks and discard them after leaving the room. Waste management should align with WHO protocols, segregating waste by category. Waste from symptomatic patients, including used masks, tissue paper, and sputum boxes, must be treated as infectious waste. Proper personal protective equipment, including N95 or surgical masks, gloves, and shoes, should be worn by personnel handling waste. Incineration or autoclaving ensures proper disposal, particularly for instruments requiring disinfection due to the high intrinsic resistance of mycobacteria. Health care facility policies should clearly outline cleaning, disinfection, or sterilization requirements based on infection risk and item use. The cleaning of the isolation room and OPD should be done with a wet Mop using at least two bucket system to timely disinfect and use the mop for cleaning the TB unit. The usage of local brooms are not allowed as they may result in aerosolization of germs.

Effective disinfection relies on factors like organism count, concentration, contact time, and organic matter. Recommended disinfectants for TB labs include phenols, chlorine, or alcohol-based solutions, selected based on material compatibility. However, phenol, effective at a 5% concentration in water, can cause irritation and toxicity upon inhalation or contact, making phenol derivatives preferable.

Chlorine, found in sodium hypochlorite, is effective but corrosive to metals. Ethanol or isopropyl alcohol at a 70% concentration is recommended for routine decontamination, with proper storage and labeling to prevent evaporation.

Peracetic acid offers swift antimicrobial action with minimal residue, making it suitable for equipment decontamination before disposal. Stable 2% solutions last 48 hours, providing a reliable option for disinfection protocols.

Overall, adherence to standardized protocols, proper waste management, and selection of appropriate disinfectants are essential components of infection control, minimizing the risk of TB transmission in health care facilities and communities.

10.5 Surveillance of TB disease among health workers

Surveillance of TB among health care workers (HCWs) is crucial to assess the effectiveness of infection prevention and control (IPC) plans. All facility staff must participate in TB medical surveillance programs as guided by the Occupational Health and Safety Act.

This comprehensive program comprises several key components:

- Pre-employment medical: New HCWs undergo baseline screening and testing for M. tuberculosis infection before employment. This establishes a baseline for comparison and

identifies high-risk individuals (e.g., those with HIV or diabetes) for appropriate placement and early treatment initiation.

- Periodic medical: **HCWs undergo TB screening and testing every six months** (and maximum on annual basis), including during outbreak investigations, to monitor their health status.
- Exit medical: Screening and testing for TB disease are conducted when HCWs leave the facility to detect any undiagnosed TB and ensure prompt treatment.
- Additionally, staff receive training on TB medical surveillance programs, and education emphasizes the importance of utilizing these services. This structured approach ensures ongoing monitoring of HCWs' TB status, facilitating early detection, treatment, and prevention of TB transmission within health care settings

Chapter 11

Monitoring and Evaluation

11. Monitoring and Evaluation

The purpose of the Monitoring and Evaluation (M&E) Guidelines is to offer essential directions for users. These guidelines aim to assist monitoring and evaluation teams in developing the most appropriate and effective tools for conducting the monitoring and supervision of TB service delivery. Additionally, they support TB performance review meetings at all levels. Users of the Guidelines are expected to conduct each TB activity in accordance with the established Standard Operating Procedures (SOPs).

This chapter of the M&E Guidelines provides specific information to all stakeholders to facilitate effective M&E under the National Tuberculosis Program (NTP) and Provincial Tuberculosis Program (PTP), as well as other stakeholders. If necessary, the Public-Private Mix (PPM) can develop separate M&E guidelines for specific initiatives. The PPM may also undertake M&E activities for projects based on the requirements of the relevant donor(s).

11.1 Objective

The objective of monitoring and supervision is to provide regular and timely updates on the implementation as well as to identify any corrective actions needed for effective and efficient implementation of the TB initiatives.

- Ensure consistent and prompt updates on the implementation of TB initiatives.
- Detect necessary corrective actions to enhance the effectiveness and efficiency of TB initiative implementation.
- Enhance the TB health care service delivery system and services through performance monitoring.
- Assess and report on key performance indicators to monitor and improve TB health care services.

11.2 M&E System

The Monitoring and Evaluation (M&E) system at the national, provincial, and district levels comprises dedicated teams responsible for overseeing program activities. At the district level, TB staff play a crucial role in supporting regular monitoring and supervision efforts. The foundation of the M&E system is the DHIS-2 case-based data collected from all TB health facilities.

Monitoring is defined as the continuous review of TB program implementation to identify and address problems, ensuring that activities are carried out accurately and effectively. This process involves the systematic collection and analysis of data and information related to various aspects of the TB program.

Supervision, on the other hand, entails overseeing or observing the performance of tasks or activities by staff to ensure they are executed correctly. Supervisors achieve this by observing activities, asking questions, providing guidance, and taking necessary actions in consultation with the staff involved.

While monitoring focuses on quantifiable aspects of the program, supervision addresses the performance of TB service providers. Despite their distinct focuses, monitoring and supervision are

interconnected; supervision often involves an element of monitoring, while monitoring does not inherently include a supervisory component.

Both monitoring and supervision will be conducted in accordance with national, provincial and district levels monthly plans. These activities will be guided by structured checklists designed to cover all dimensions of the program and its various interventions. This comprehensive approach ensures the effective implementation and continuous improvement of TB initiatives.

Table 45*: Logical M&E Framework*

Input	Process (Activities)	Output (Strategic direction)	Outcome (Objectives)	Impact (Goal)
Program inputs refer to the set of resources: ○ Human Resources ○ Financial Resources ○ Equipment ○ Supplies ○ Record Keeping	**Program processes refer to the set of activities in which program inputs are utilized in pursuit of the results expected from the program.** ○ Lab Diagnostics ○ Management & Technical Trainings ○ Drug Management ○ Awareness creation	**Program outputs are the results obtained at the program level through the execution of activities using program resources.** ○ Enhanced Diagnostics and Treatment services ○ Improved knowledge ○ Persons trained ○ Service outputs ○ Service utilization	**Progress outcomes are the set of results expected to occur at the population level due to program activities and the generation of program outputs.** ○ Targeted Outcomes ○ Case notification rate (CNR) and treatment success rate (TSR)	**What and how much change occurred at the program or population level that is attributable to the program** ○ Targeted impact on disease burden, incidence and mortality

11.3 Indicators in Monitoring and Evaluation

11.3.1 Input Indicators:

These indicators measure the quantity and quality of resources provided for project activities. Examples include finance, human resources, training, equipment, materials, and supplies. Specific inputs like reagents, medicine, health education materials, training for various cadres, guidelines, and manuals are also included.

11.3.2 Process Indicators:

These indicators measure the appropriateness of applying project resources according to the plan, considering factors such as timing, quantities, and quality. They assess whether activities are leading to the expected outputs. Indicators in this category include processes like presumptive identification, referral to labs & X-pert and BSL labs, sputum transportation mechanisms, various measures of active case finding, and intervention-specific indicators.

11.3.3 Output Indicators:

These indicators measure the quantity or quality of products or services created or provided through the use of inputs. Examples include the number or percentage of products, knowledge, information, changes, and benefits. This category includes intermediate factors linking inputs to expected outputs. TB data collected and analyzed for output indicators includes case detection of DS, DR, and pediatric TB, as well as the treatment success rate of various types of cases. Intervention-specific output indicators are also included.

11.3.4 Impact Indicators:

These indicators refer to the incidence and prevalence of different types of tuberculosis and TB-related mortality. They are not calculated routinely. Data collected through routine recording and reporting systems is analyzed by epidemiologists, typically at the national level, to measure these indicators.

11.4 M&E Components

The M&E system of TB program consists of the following two components:

- **Recording, Reporting, and Feedback System:**
  This component involves the systematic documentation of program activities, the reporting of collected data of TB patients, and the provision of feedback to relevant stakeholders. It ensures that accurate and timely information is available for decision-making and program adjustments.
- **Monitoring and Supervision of TB Service Delivery and Validation of TB Indicators Data:**
  This component includes the ongoing monitoring and supervision of TB service delivery to ensure adherence to standards and protocols. It also involves the validation of TB indicators data to verify its accuracy, completeness and timeliness, ensuring that the data reflects true program performance and outcomes.

11.4.1 Data recording, reporting and feedback system

11.4.1.1 DHIS-2 Overview

DHIS-2 is a comprehensive tool designed for the collection, validation, analysis, and presentation of both aggregate and patient-based statistical data. It supports integrated health information management activities and is recommended and agreed upon by all programs for reporting surveillance data on a common dashboard.

11.4.1.2 Implementation of DHIS-2 Tracker

Recently, the DHIS-2 Tracker for capturing case-based TB data has been rolled out in Pakistan. Training sessions on the DHIS-2 TB Tracker and the distribution of laptops to representatives of TB facilities were conducted in the provinces of Baluchistan, Sindh, and KP, as well as the regions. The DHIS-2 TB tracker was piloted in Islamabad Capital Territory (ICT) during the first three quarters of 2023 and subsequently rolled out in Baluchistan, KP, Sindh, Azad Jammu and Kashmir (AJK), and Gilgit-Baltistan (GB) regions from the fourth quarter of 2023 onwards.

However, the Pakistan Epidemiological Review Report 2022 highlighted that the DHIS-2 tracker piloted in Pakistan lacked key recommended components, such as a laboratory module, and **was not aligned with the latest WHO TB tracker**.

11.4.1.3 Programmatic Management of Drug-Resistant TB (PMDT) Sites

At PMDT sites, individual case-based data is entered electronically at the facility level and shared at the provincial and national levels. This data is managed using an Excel-based Electronic Nominal Recording Reporting System (ENRS), which captures data on confirmed drug-resistant TB (DRTB) cases throughout the entire cascade of care, from notification to monitoring service provision and treatment outcomes. A significant challenge is the lack of integration between the DHIS-2 and ENRS systems, despite their parallel use. There is a pressing need to integrate these two systems.

11.4.1.4 Recording and Reporting Tools at TB Health care Facilities

At TB health care facilities, several recording and reporting tools are employed for record-keeping and reporting. Case-based data is also entered into the DHIS-2 system. These tools ensure that accurate and timely data is available for effective monitoring and evaluation of TB programs. List of data recording and reporting tools is available in Table 46.

Table 46: ***List of Data Recording and Reporting Tools***

Forms	Description	Type
TB 01	Tuberculosis treatment card (BMU based)	Recording Tool
TB 02	Tuberculosis Identity card (patient card)	Recording Tool
TB 03	BMU Tuberculosis register	Recording Tool
TB 04	TB laboratory register	Recording Tool
TB 05	Request for Xpert and AFB Microscopy Examination	Recording Tool
TB 07	Quarterly report on Tuberculosis case registration	Reporting tool
TB 09	Quarterly report on treatment outcome	Reporting tool
TB 10	Transfer/ referral form	Recording Tool

The Standard Operating Procedures (SOPs) for data validation arrangement and timeline are shown below:

Table 47: ***Data validation mechanism in place in Pakistan, periodicity and human resources required***

Level	Arrangements	Periodicity	Key Facilitator
Facility	Public sector: District TB Officers (DTOs) are responsible for surveillance activities through case based DHIS2	Ongoing every month	• DTC/DTO • SLS/DLS/ Cross checker
District	Private sector: Holds Quarterly Review Meetings (QRM) at the end of each reporting quarter for data validation and updating on monitoring visits' findings	Quarterly	• DFS/ DTC/DTO • SLS/DLS/ Cross checker
Province	Inter-district meeting: This is a two-day meeting at the provincial level to evaluate and analyze district's performance and consider whether it is necessary to take corrective actions	Quarterly / Bi-annually	• Provincial/Regional Manager for TB control • In charge Provincial Reference Lab – Senior Provincial Program Officer – DTOs/PPOs • Representative from NTP • M&E persons of specific TB components
National	Inter-provincial meeting: This is a two-day activity meant for critical review of the performance, gap identification, and evidence-based planning	Quarterly	• National Coordinator CMU/Deputy National Coordinator NTP • M&E and surveillance team at NTP/CMU • Focal persons from PRL • International partners from WHO & USAID

Monitoring and Supervisory (M&S) System

In conducting the monitoring and supervision of the TB program activities, the district health office, the provincial TB program, and the national TB program, all carry out quarterly site monitoring visits for all Basic Management Units (BMUs) and Programmatic Management of Drug-resistant Tuberculosis (PMDT) sites. About 50 percent of the implementation units of the lower tiers are also supervised and monitored by these teams.

11.4.1.5 Monitoring of PPM facilities

Monitoring of public-private mix (PPM) facilities is mainly the responsibility of the district health team. The team is comprised of the District TB Coordinator and the District Laboratory Supervisor who both conduct field monitoring of PPM health facilities and laboratories. Provincial and national teams are also mandated to conduct field monitoring of PPM facilities.

11.4.1.6 Qualified Monitoring Team

A dedicated team of health managers with technical skills, knowledge, and motivation is essential to improve the quality of services. The monitoring and supervisory teams have already been designated at the national, provincial, and district levels, as follows:

- National Level:
    - Monitoring and Surveillance Officers
    - Focal Person PRL
- Provincial Level:
    - Deputy Director CDC
    - Monitoring Officers CDC
    - Provincial Lab Monitoring Officer
    - Senior Lab Supervisor (SLS)
    - Senior Provincial Program Officers GF
- District Level:
    - District Health Officer (DHO)
    - Deputy DHO
    - Assistant DHO
    - District TB Coordinator (DTC)
    - District TB Officer (DTO)
    - District Lab Supervisor (DLS)

11.4.1.7 Standardized Monitoring and Supervisory Tools

To ensure consistency and effectiveness in monitoring, standardized tools and methods need to be developed and utilized across all levels of the TB program. These tools should be aligned with the overall objectives of the M&S system and facilitate accurate data collection and analysis.

11.4.1.8 Adequate Resources

The monitoring teams must be equipped with the necessary resources to carry out their duties effectively. This includes funding for travel to various health facilities and laboratories, as well as the technological resources needed to collect, store, and analyze data. Access to modern tools such as the proposed mobile application and online dashboard will be crucial in supporting their efforts.

11.4.1.9 Monitoring and Supervisory Visits

The District, Provincial TB Program (PTP), and National TB Program (NTP) staff will conduct Monitoring and Supervisory (M&S) visits to health facilities. These visits aim to promote the quality of services by strengthening relationships within the system and focusing on identifying and resolving problems.

- **Purpose of M&S Visits**

  The TB M&S tools and protocols enable Monitoring and Supervision managers to observe service quality and validate performance reports. Routine monitoring helps supervisors become familiar with individual staff, their aptitudes, the community, and the facility, allowing for better performance monitoring over time. This process aids in identifying and addressing problems to enhance service quality.

- **Activities During M&S Visits**

  M&S visits will ensure the proper use of recording and reporting tools and verify data transfer accuracy. The RR tools and protocols allow TB Supervisory staff to observe the quality of data recorded in the prescribed tools and validate it against reporting tools. Routine monitoring facilitates supervisors in understanding individual staff capabilities, community dynamics, and facility operations, leading to improved service quality over time.

  These visits also help in identifying and discussing data management difficulties or misunderstandings, providing opportunities for learning.

  During visits to health facilities or communities, supervisors will:

  - Maintain respect and patience throughout the supervisory visit.
  - Use the checklist contained in the plan to observe and gather information. The tool/checklist must be filled out completely according to the user guidelines.
  - Pay attention to the issues and challenges faced by the staff.
  - Offer constructive feedback on performance.
  - If a register is filled incorrectly, demonstrate the correct procedure.
  - Inform supervisees about any new guidelines and information.
  - Provide training on new guidelines if required.
  - Highlight areas that need improvement or strengthening.
  - Note issues that could not be resolved at the district level and propose support required

from higher levels to solve these problems.

- Submit an online monitoring and supervisory activity report to the relevant manager.
- Mark the visit in the health facility registers as evidence of the monitoring visit.

By following these guidelines, M&S visits will ensure consistent quality improvement, effective problem resolution, and continuous learning and development within the TB program.

Table 48*: Standard Operating Procedure for M&E Visits*

SOPs for M&S visits

1.IDENTIFY A HEALTH MANAGEMENT TEAM

The following persons should be part of the M&S Team at District Level:

- District Health Officer (DHO)/ADHS/
- Program Focal Persons of TB (DTC)
- District TB Officer (DTO)
- Lab In-charge

2. PREPARE FIELD VISIT PLAN

Supervisory teams will prepare online monthly tour plans & submit these online to the Competent Authority for approval

The following must be a part of the visit/tour plan:

- Number of visits; Date of the visits; Name of the health facilities/outreach staff to be visited; Purpose of the visits; Tool(s) to be used during visits
- Prepared performance report of previous three months of the HF and keep it handy
- The Competent Authority may review and approve plans made by adjusting dates, drivers and vehicles
- After the approval of the tour plan, the supervisor will:
- Follow the approved field visit program
- Share the visit plan with the health facilities and outreach workers beforehand as possible or at least upon arrival, as per requirement
- Retain a copy of approved tour/visit plan

3. ARRANGE MONITORING TOOLS, GUIDELINES & PROTOCOLS

- Download last monthly performance report from the online MIS
- Checklists should be completed for each of the facilities to be visited

4. ARRANGE M&S VISIT RESOURCES

The main resources required are:

- Reliable transport
- Adequate time for preparation, travel, field visit, reporting and follow up activities
- Monitoring and supervisory tools /checklists
- Support for periodic review meetings

5. CONDUCT MONITORING & SUPERVISORY VISIT

During the visit, the supervisor will:

Apply the level-specific checklist, as contained in tour plan. The tool/checklist has to be filled completely according to the given user guidelines

- Provide hands-on support and feedback
- Mark evidence of monitoring visit, such as marking the facility attendance register,
- Provide written feedback to the staff in the visitor's book of the facility, which must be signed by both monitor & concerned staff. Formal feedback must be provided to concerned health facility/staff under a covering letter, where necessary

6. REPORT AND PROVIDE FEEDBACK TO HF STAFF AND RELEVANT COMPETENT AUTHORITY

- After the visit, the supervisors will provide support and strengthen capacity of health care providers to meet performance goals
- The Competent Authority will review the report and provide feedback within 1 week, on following aspects:
- Direct the supervisor for further actions needed with a timeline to undertake actions
- Instruct concerned focal person/manager on the issues identified and actions required from them
- In the next visit, supervisor should check/observe the follow up of actions of previous visit Present consolidated M&S activity report of the district in the monthly/quarterly review meetings for decision making for resolution of issues

11.4.1.10 Review Meetings

In addition to M&S visits, TB program review meetings are held quarterly at provincial and national levels. At the district level, the District TB Coordinator (DTC) or District TB Officer (DTO) cross-checks and validate data at individual Basic Management Units (BMUs) and facilitate quarterly review meetings with private sector providers for data validation and program updates.

- **District TB Review Meeting**

District TB review meetings are primarily designed for data validation. Medical officers, paramedics (TB facilitators), and lab technicians from BMUs in the district gather at the district headquarters for a one-day meeting. They bring recording instruments (TB01, TB03, and TB04) and reports (TB07 and TB09) for validation by the DTC with technical support from Provincial Program Officers (PPOs) or experts from the province. The meetings are chaired by the District Health Officer (DHO), who is informed of achievements and shortcomings and is expected to support BMUs in resolving administrative problems. It is important to include the following aspects of the facilities made part of the district monthly review meetings.

Standard District Monthly/Quarterly Review Agenda:

- Presentation of findings from monthly monitoring and supervisory visit reports
- TB facility staff absenteeism and transparency
- Analysis of performance data on the online dashboard
- Identification of high and low-performing TB facilities
- Availability of medicines, supplies, and equipment
- Data validation reports
- Performance improvement methods and techniques
- Other relevant issues

- **Provincial TB Review Meeting**

Provincial review meetings are convened quarterly at the provincial headquarters following the completion of district meetings in all districts. The Provincial TB Officer (PTO)Senior Provincial Program Officer presents district-wise performance data and shares trend analyses. The meeting is attended by the Director General Health of the province and attended by the senior health management of the province & senior officials of CMU. These meetings aim to review the performance of districts in the preceding quarter, discuss issues and challenges, and make decisions on how to improve performance. A planning/action matrix is developed to follow-up the decisions taken.

- **National TB Review Meeting**

National review meetings are held at the federal level after the completion of Provincial TB program Review meetings in all provinces. Aggregated national data is shared with Provincial TB Programs (PTPs) and partners. Trend analyses are conducted, and group work is undertaken to address programmatic gaps. A planning /action matrix is developed to follow-up the decisions taken.

Key Objectives of Review Meetings:

- Ensuring the accuracy and reliability of data through comprehensive validation processes.
- Reviewing performance data to identify trends, high and low performers, and areas needing improvement.
- Discussing challenges and issues identified at various levels and formulating solutions.
- Providing a forum for making informed decisions to enhance TB program performance.
- Facilitating communication and coordination among various stakeholders to support TB program goals.

Table 49*: Data Quality Attributes*

S. No.	Parameter	Explanation
1.	Case definitions	TB case definitions are standardized and consistent with NTP adopted WHO guidelines
2.	Data variables	TB surveillance system is designed to capture a minimum set of variables for all reported TB cases
3.	Data Accuracy:	The data measure what they are intended to measure
4.	Reliability	The measures do not change according to who is using them and when or how often they are used
5.	Precision	The data have the necessary detail
6.	Completeness	The data is all inclusive and not partial
7.	Timeliness	Data is up-to-date and available on time
8.	Integrity	There is no deliberate bias or manipulation in data collection.
9.	Confidentiality	Clients are assured that their data will be maintained according to national and/or international standards for data
10.	Data security	The TB data must have controls to secure the clients data

Table 50*: TB-Top Ten Priority Indicators*

Priority indicators	End TB Strategy target 2025
1. TB treatment coverage	≥ 90%
2. TB treatment success rate	≥ 90%
3. Percentage of TB-affected households that experience catastrophic costs due to TB	0%
4. Percentage of new and relapse TB patients tested using a WHO-recommended rapid tests (WRD) at the time of diagnosis	≥ 90%
5. LTBI treatment coverage	≥ 90%
6. Contact investigation coverage	≥ 90%
7. Drug susceptibility testing (DST) coverage for TB patients	100%
8. Treatment coverage, new TB drugs	≥ 90%
9. Documentation of HIV status among TB patients	100%
10. Case Fatality Ratio (CFR)	0%

Table 51: *List of additional Indicators*

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
TB Detection Rate (Treatment Coverage)	**Core**	Percent of people with new and relapse TB and with unknown previous TB treatment history (all forms) who were notified during the reporting period, out of the estimated number of people with incident TB for that year. Note: This indicator is also referred to as "Treatment Coverage Rate"; the name is updated to TB detection rate here to emphasize that treatment coverage is not represented in this data. Calculation: (Numerator/Denominator) x 100	Number of people with new and relapse TB (and with unknown previous TB treatment history), all forms (bacteriologically confirmed plus clinically diagnosed, pulmonary and extra pulmonary), who were notified in the reporting period.	Estimated incidence of TB (all forms) in the same reporting period	Age (<15, 15+), sex
Percent Bacteriologically Confirmed	**Core**	Percent of people with new and relapse pulmonary TB who are bacteriologically confirmed. Bacteriologically confirmed: Smear positive for TB or culture positive for TB or positive for TB by a World Health Organization-recommended rapid diagnostics test (WRD): FluoroType® MTBDR (Hain), Loopamp™ MTBC detection kit (TB-LAMP), Xpert® MTB/RIF, Xpert® MTB/RIF Ultra, Truenat® MTB or MTB Plus, RealTime MTB (Abbott), BD MAX™ MDR-TB, cobas® MTB (Roche), or LF-LAM. Note: LF-LAM is included as a recommended TB test for people living with HIV (PLHIV). LF- LAM is not recommended to confirm TB in all populations and notably should not be used in outpatient settings for adults,	Number of new and relapse bacteriologically confirmed pulmonary TB notifications (smear positive or culture positive or positive by WRD during the reporting period)	Number of people with new and relapse pulmonary TB (bacteriologically confirmed plus clinically diagnosed) during the reporting period	Age (0–4, 5–14, 15+), sex, HIV status

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
		adolescents, and children without symptoms of TB or in those with a CD4 count > 200 cells/mm3. At the time of this publication, Alere Determine™ TB LAM Ag is the only commercially available LF- LAM test. Full guidance on the use of LF-LAM can be found at: www.who.int/publications/i/item/9789241550604 Calculation: (Numerator/Denominator) x 100			
Childhood TB Notifications	**Core**	Number of children and adolescents (0–14 years) with new and relapse TB or with unknown previous TB treatment history, all forms, who were notified in a reporting period	Number of children and adolescents (0–14 years) with new and relapse TB or with unknown previous TB treatment history, all forms, who were notified in a reporting period	N/A	Age (0–4, 5–9, 10–14), sex, HIV status
RR/MDR-TB Notifications	**Core**	Number of people with rifampicin-resistant (RR) and multidrug-resistant (MDR) TB notified during the reporting period. RR/MDR-TB: RR-TB is TB caused by Mycobacterium Tuberculosis (M. tuberculosis) strains that are resistant to rifampicin; MDR-TB strains are resistant to at least both rifampicin and isoniazid.	Number of people with RR-TB and MDR-TB notified during the reporting period	N/A	Age (<15, 15+), sex
Private Sector TB Notifications	**Core**	Number of people with new and relapse TB of all forms (bacteriologically confirmed plus clinically diagnosed) notified by private non-national TB program (NTP) providers in the reporting period. Per the WHO's definition/ database, private non-NTP providers include private individual and institutional providers, corporate/business sector providers, mission hospitals, and other clinics or hospitals managed by nongovernmental organizations (NGOs) and faith-based organizations.	Number of people with new and relapse TB of all forms (bacteriologically confirmed plus clinically diagnosed) notified by private non-NTP providers in the reporting period	N/A	Age (<15, 15+), sex
Percent of Contacts Screened for TB	**Core**	Percent of contacts of people with bacteriologically confirmed pulmonary TB (index cases) who were screened for active TB disease, among all contacts identified during the reporting period. Contact investigation (CI) is a systematic process to identify people (contacts) who were exposed to active pulmonary TB disease; assess contacts for signs or symptoms of active TB disease, provide diagnostic testing to confirm or exclude active disease or diagnose TB infection, and provide contacts with treatment for TB disease or infection. CI consists of identification of contacts, prioritization of contact at highest risk, clinical evaluation, and diagnostic testing and treatment as clinically indicated. Calculation: (Numerator/Denominator) x 100	Number of contacts of people with notified new and relapse bacteriologically confirmed pulmonary TB who were screened for active TB disease during the reporting period	Number of contacts of people with notified new and relapse bacteriologically confirmed pulmonary TB identified during the reporting period	(0–4, 5–14, 15+), sex

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
DS-TB Treatment Success Rate	**Core**	Percent of people with new and relapse drug-sensitive tuberculosis (DS-TB) (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary) who were notified in a specified period that were cured or treatment completed, among the total people with new and relapse TB who were initiated on treatment during the same reporting period (excluding those moved to RR-TB treatment cohort). Treatment outcomes are defined by the time period of initiation on treatment; e.g., "2018 cases successfully treated" reflect those who were initiated on treatment in 2018, even though treatment may have extended into 2019. For this reason, reports of treatment outcome data lag by one year. Calculation: (Numerator/Denominator) x 100	Number of people with new and relapse DS-TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary), who were registered in a specified period that were cured or treatment completed	Number of people with new and relapse DS-TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary) who initiated treatment in the same period	Age (<15, 15+), sex, HIV status
DR-TB Treatment Success Rate	**Core**	Percentage of people with drug-resistant tuberculosis (DR-TB) (rifampicin-resistant [RR]-TB/multidrug-resistant [MDR]-TB, pre-extensively drug-resistant [pre-XDR]-TB, and extensively drug-resistant [XDR]-TB) successfully treated (cured or treatment completed) among all people with DR-TB who were initiated on treatment during the reporting period. Treatment outcomes are defined by the time period of initiation on treatment; e.g., "2018 cohort successfully treated" reflect those who were initiated on treatment in 2018, even though treatment may have extended into 2020. For this reason, reports of treatment outcome data lag by 2 years. Calculation: (Numerator/Denominator) x 100	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) who were cured or treatment completed during the reporting period	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB)who were initiated on DR-TB treatment during the same reporting period	Age (<15, 15+), sex
TPT Initiations	**Core**	Number of people who were initiated on TB preventive treatment (TPT). This includes: (1) household and other close contacts of people with notified, bacteriologically confirmed pulmonary TB (adults, adolescents, and children <5 years), and (2) people living with HIV (PLHIV). Household contact: a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the initiation of current treatment. "Other" close contacts will be assessed by clinical judgment or experience. In general, this may include someone who may not live in the same house as the index patient but spends considerable time there or spent time elsewhere when	Number of people who were initiated on TPT during the reporting period, which includes: Household and other close contacts of people with notified, bacteriologically confirmed TB (5 plus and children <5), and PLHIV	N/A	Age (0–4, 5–14, 15+), sex, risk group (contacts, PLHIV)

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
		the index case was present. It may also be someone who the index case may have spent time in close contact in other settings such as in school or in the workplace.			
Percent of TB Financing Received from Domestic Sources	**Core**	Percent of an NTP's budget received from domestic sources during the reporting period. Calculation: (Numerator/Denominator) x 100	The amount of the NTP's budget received from domestic sources (including loans) during the reporting period (in U.S. dollars)	The amount of an NTP's budget received from all sources (domestic; the Global Fund to Fight AIDS, Tuberculosis and Malaria; USAID; and other sources) during the reporting period (in U.S. dollars)	N/A
Rapid diagnostic testing at time of initial diagnosis	**Core Plus**	Percent of people with new and relapse TB who were tested using a WHO-recommended rapid diagnostic test (WRD): FluoroType® MTBDR (Hain), Loopamp™ MTBC detection kit (TB-LAMP), Xpert® MTB/RIF, Xpert® MTB/RIF Ultra, Truenat® MTB or MTB Plus, RealTime MTB (Abbott), BD MAX™ MDR-TB, cobas® MTB (Roche), or LF-LAM at the time of initial TB diagnosis (regardless of test result). Calculation: (Numerator/Denominator) x 100	Number of people with new and relapse TB notified during the reporting period who were tested using a WRD: FluoroType® MTBDR (Hain), Loopamp™ MTBC detection kit (TB-LAMP), Xpert® MTB/RIF, Xpert® MTB/RIF Ultra, Truenat® MTB or MTB Plus, RealTime MTB (Abbott), BD MAX™ MDR-TB, cobas® MTB (Roche), or LF-LAM (regardless of test result).	Number of people with notified new and relapse TB during the reporting period	Age (0–4, 5–14, 15+), sex, type of diagnostic test
Percent of people with new and relapse TB with drug susceptibility testing (DST)	**Core Plus**	Percent of people with new and relapse pulmonary TB who have drug susceptibility testing (DST) results for 1) rifampicin, 2) isoniazid, 3) fluoroquinolones, 4) bedaquiline, and 5) linezolid Calculation: (Numerator disaggregate: DST type (1,2,3,4 or 5*)/Denominator) x 100 *Note 5 separate proportions should be calculated, one for each drug type.	Number of people with new and relapse pulmonary TB who have drug susceptibility test (DST) results for 1) rifampicin, 2) isoniazid, 3) fluoroquinolones, 4) bedaquiline, and 5) linezolid	Number of people with bacteriologically confirmed new and relapse pulmonary TB	DST type: rifampicin fluoroquinolones isoniazid-bedaquiline linezolid Age (0–4, 5–14, 15+), sex, HIV status

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
Percent of people with previously treated TB with drug susceptibility testing (DST)	**Core Plus**	Percent of people with previously treated (including relapse) pulmonary TB who have DST results for 1) rifampicin, 2) isoniazid, 3) fluoroquinolones, 4) bedaquiline, and 5) linezolid Calculation: (Numerator disaggregate: DST type (1,2,3,4 or 5*)/Denominator) x 100 *Note 5 separate proportions should be calculated, one for each drug type.	Number of people with previously treated (including relapse) pulmonary TB who have drug susceptibility test (DST) results for 1) rifampicin, 2) isoniazid, 3) fluoroquinolones, 4) bedaquiline, and 5) linezolid	Number of people with bacteriologically confirmed previously treated (including relapse) pulmonary TB	DST type: rifampicin fluoroquinolones isoniazid-bedaquiline linezolid Age (0–4, 5–14, 15+), sex, HIV status
Pre-XDR/XDR Notifications	**Core Plus**	Number of people with pre-extensively drug-resistant (pre-XDR) and extensively drug-resistant (XDR) TB notified during the reporting period. Pre-XDR/XDR-TB: XDR-TB is caused by a strain of M. tuberculosis complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other “Group A” drug (bedaquiline or linezolid); pre-XDR-TB meets these qualifications but is resistant to a fluoroquinolone or a “Group A” drug, but not both.	Number of people with laboratory-confirmed or clinically diagnosed drug-resistant (DR)-TB (RR/MDR-TB and pre-XDR/XDR-TB) who initiated treatment for DR-TB during the reporting period.	N/A	Age (<15, 15+), sex
DR-TB treatment initiations	**Core Plus**	Number of people with laboratory-confirmed or clinically diagnosed DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) who initiated treatment for DR-TB during the reporting period. RR/MDR-TB: RR-TB is TB caused by Mycobacterium Tuberculosis (M. tuberculosis) strains that are resistant to rifampicin; MDR-TB strains are resistant to at least both rifampicin and isoniazid. Pre-XDR/XDR-TB: XDR-TB is caused by a strain of M. tuberculosis complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other “Group A” drug (bedaquiline or linezolid); pre-XDR-TB meets these qualifications but is resistant to a fluoroquinolone or a “Group A” drug, but not both.	Number of people with laboratory-confirmed or clinically diagnosed DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) who initiated treatment for DR-TB during the reporting period	N/A	Age (<15, 15+), sex, HIV status
DR-TB "all oral" short treatment regimen initiations	**Core Plus**	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) initiated on “all oral” short treatment regimen during the reporting period. "Short treatment regimens" refer to regimens with a duration of 12 months or less.	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) initiated on "all oral" short treatment regimen during the reporting period	N/A	Age (<15, 15+), sex

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
DR-TB "all oral" longer treatment regimen initiations	**Core Plus**	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) who initiated an "all oral" longer treatment regimen during the reporting period. "Longer treatment regimens" refer to regimens with a duration of 14 months or more, usually lasting 18–24 months.	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) who initiated an "all oral" longer treatment regimen during the reporting period	N/A	Age (<15, 15+), sex
Number of people with adverse reactions to DR-TB treatment	**Core Plus**	Number of people on DR-TB treatment (RR/MDR-TB and pre-XDR/XDR-TB) who developed at least one adverse drug reaction (ADR) to DR-TB treatment during the reporting period; this includes all people on treatment during the specified reporting period and is not related to a cohort. An ADR (sometimes referred to as an "adverse event") is any negative medical occurrence that may present in a person with TB during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment. More information on monitoring of ADRs in DR-TB can be found here, and information on ADR grading can be found at https://rsc.niaid.nih.gov/sites/default/files/corrected-grading-table-v-2-1-with-all-changes-highlighted.pdf.	Number of people on DR-TB treatment (RR/MDR-TB and pre-XDR/XDR-TB) who developed at least one ADR to DR-TB treatment during the reporting period; this includes all people on treatment during the specified reporting period and is not related to a cohort.	N/A	Age (<15, 15+), sex, type of adverse reaction (e.g., vomiting, dizziness, reduced appetite, gastritis)
TPT initiations among contacts	**Core Plus**	Number of household contacts and other close contacts of people with bacteriologically confirmed, notified pulmonary TB who initiated TB preventive treatment (TPT) during the reporting period. This indicator is a subset of the core indicator "TPT initiations." "Other" close contacts will be assessed by clinical judgment or experience. In general, this may include someone who may not live in the same house as the index patient but spends considerable time there or spent time elsewhere when the index case was present. It may also be someone who the index case may have spent time in close contact in other settings such as in school or in the workplace.	Number of adult, adolescent, and children <5 years who are household or other close contacts of people with bacteriologically confirmed, notified pulmonary TB who initiated TPT during the reporting period	N/A	Age (0–4, 5–14, 15+), sex, public vs private
TPT Completions	**Core Plus**	Number of contacts or other eligible people who completed TPT during the reporting period. During a given reporting period, the cohort of people who initiated TPT should be tracked to monitor the number who complete TPT. Completion data should be disaggregated by: * Household contacts aged <5 years * Household contacts 5 years and up * People living with HIV (PLHIV)	Number of contacts or other eligible people who completed TPT during the reporting period	N/A	Age (0–4, 5–14, 15+), sex, risk group (contacts, PLHIV)

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
Existence of a national or social health insurance system whose benefit package includes TB clinical services	**Core Plus**	Country has a national or social health insurance (NHI/SHI) scheme whose benefit package includes TB clinical services. National/social health insurance: forms of health insurance that are often administered by the government or a quasi-governmental agency, funded through contribution from taxes and/or employers and employees, and cover a package of services. Community based health insurance (CBHI) schemes are usually voluntary and characterized by community members pooling funds to offset the cost of health care.	0 = EITHER No national/social health insurance scheme OR national/social health insurance available but DS-TB & DR-TB (diagnosis and treatment costs) are excluded 2 = National/social health insurance is available and includes diagnosis and treatment costs for DS- or DR-TB but not both 4 = National/social health insurance is available and includes diagnosis and treatment costs for both DS- and DR-TB	N/A	N/A
Percent children and adolescents (0–14 years old) with new and relapse pulmonary TB who are bacteriologically confirmed	**National Level**	Percent of children and adolescents (0–14 years) with new and relapse pulmonary TB who are bacteriologically confirmed. Bacteriologically confirmed: Smear positive for TB or culture positive for TB by a World Health Organization-recommended rapid diagnostics test (WRD): FluoroType® MTBDR (Hain), Loopamp™ MTBC detection kit (TB-LAMP), Xpert® MTB/RIF, Xpert® MTB/RIF Ultra, Truenat® MTB or MTB Plus, RealTime MTB (Abbott), BD MAX™ MDR-TB, cobas® MTB (Roche), or LF-LAM. Note: This is a subset of the core indicator "Percent Bacteriologically Confirmed." Calculation: (Numerator/Denominator) x 100	Number of children and adolescents (0–14 years) with new and relapse pulmonary TB who are bacteriologically confirmed during a reporting period	Number of children and adolescents (0–14 years) with new and relapse pulmonary TB during the reporting period	Age (0–4, 5–14), sex
MDR-TB notifications among children and adolescents (0-14 years)	**National Level**	Number of children and adolescents (0–14 years) with rifampicin-resistant (RR)-TB/multidrug-resistant (MDR)-TB notified during the reporting period; pre-extensively drug-resistant (pre-XDR) TB, and extensively drug-resistant (XDR) TB should not be reported in addition to the RR/MDR-TB notifications. RR/MDR-TB: is TB caused by Mycobacterium Tuberculosis (M. tuberculosis) strains that are resistant to rifampicin; MDR-TB strains are resistant to at least both rifampicin and isoniazid. Note: pre-XDR/XDR notifications should not be added to RR/MDR-TB notifications to avoid double counting of DR-TB notifications. Children who are diagnosed with pre-XDR and XDR-TB will already have been identified and recorded as having RR/MDR-TB. The number of RR/MDR-TB	Number of children and adolescents (0–14 years) with notified RR/MDR-TB during the reporting period (both lab-confirmed and clinically diagnosed).	N/A	Age (0–4, 5–14), sex

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
		notifications should therefore equal the total number of DR-TB notifications.			
Percent of people with notified TB with a contact investigation initiated	**National Level**	Percent of people with notified pulmonary TB with a contact investigation (CI) initiated. CI initiated: For the purpose of this indicator, "initiated" refers to the process of enumeration of all known contacts to an index TB case. CI will include the evaluation of those contacts to determine if any have active TB disease or TB infection (TBI) through symptom screening, diagnostic testing, chest X-ray (CXR), or clinical evaluation. Index case: Person with pulmonary TB who is notified to health authorities. Calculation: (Numerator/Denominator) x 100	Number of people with notified pulmonary TB with a CI initiated	Number of people with notified pulmonary TB during the reporting period	Age (0–4, 5–14), sex
Number of contacts with presumptive TB	**National Level**	Number of contacts to a person with notified pulmonary TB who have signs or symptoms of TB, as defined by the WHO 4 symptom screen or the NTP (i.e., have presumptive TB). Presumptive TB: a person who has one or more signs or symptoms of active TB disease and should be referred for diagnostic testing to diagnose or rule out active disease.	Number of contacts with presumptive TB	N/A	Age (0–4, 5–14), sex
Number of contacts who received TB diagnostic testing	**National Level**	Number of contacts to a person with notified pulmonary TB with signs or symptoms of TB (e.g., presumptive TB) who received diagnostic testing for TB. Diagnostic testing includes smear, culture or a World Health Organization recommended rapid diagnostics test (WRD): FluoroType® MTBDR (Hain), Loopamp™ MTBC detection kit (TB- LAMP), Xpert® MTB/RIF, Xpert® MTB/RIF Ultra, Truenat® MTB or MTB Plus, RealTime MTB (Abbott), BD MAX™ MDR-TB, cobas® MTB (Roche), or LF- LAM.	Number of contacts to a person with notified pulmonary TB who received diagnostic testing for presumptive TB	N/A	Age (0–4, 5–14), sex

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
Number of contacts diagnosed with active TB disease	**National Level**	Number of contacts diagnosed with TB disease (both bacteriologically and clinically confirmed) among all contacts who were screened for TB disease during the reporting period	Number of contacts who were diagnosed with TB disease (both bacteriologically and clinically confirmed)	N/A	Age (0–4, 5–14), sex
Number of contacts who initiated TB treatment	**National Level**	Number of contacts diagnosed with active TB disease who initiated TB treatment	Number of contacts who initiated TB treatment	N/A	Age (0–4, 5–14), sex
DS-TB treatment outcomes	**National Level**	Number of people with DS-TB (new and relapse), all forms, with each defined DS-TB treatment outcome, among the cohort of people who were initiated DS-TB treatment during a reporting period. Cohort reporting: Treatment outcomes are defined by the time of initiation on treatment; e.g., "2018 cohort successfully treated" reflect those who were initiated on treatment in 2018, even though treatment may have extended into 2019. For this reason, reports of treatment outcome data lag by one year.	Number of people with DS-TB (new and relapse), all forms, with each defined DS-TB treatment outcome (defined below), among the cohort of people who were initiated DS-TB treatment during a reporting period. DS-TB Treatment outcomes: • Successfully treated: Cure or Completed treatment • Cure • Completed treatment • Lost to follow-up (LTFU) • Treatment failed • Died • Not Evaluated	N/A (cohort size reported under core DS-TB TSR indicator)	Age (<15, 15+), sex, HIV status, treatment outcome (defined above)
DR-TB treatment outcomes	**National Level**	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) with each of the defined DR-TB treatment outcomes, among the cohort of people who were initiated on DR-TB treatment during a defined reporting period. Cohort reporting: Treatment outcomes are defined by the time of initiation on treatment; e.g., "2018 cohort successfully treated" reflect those who were initiated on treatment in 2018, even though treatment may have extended into 2019 or 2020. For this reason, reports of DR-TB treatment outcome data lag by 1–2 years.	Number of people with DR-TB (RR/MDR-TB and pre-XDR/XDR-TB) with each of the treatment outcomes (defined below), among the cohort of people who were initiated on DR-TB treatment during a defined reporting period. DR-TB Treatment outcomes: • Successfully treated: Cure or Completed treatment • Cure • Completed treatment • Lost to follow-up (LTFU) • Treatment failed • Died • Not evaluated	N/A (cohort size reported under core TSR indicator)	Age (<15, 15+), sex, HIV status, treatment outcome

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
Treatment success rate in children and adolescents (0-14 years)	**National Level**	Percent of children and adolescents (0–14 years) who were cured or completed treatment for DS-TB among the total number of children and adolescents (0–14 years) with new and relapse TB who were initiated on treatment for DS-TB during the same reporting period (excluding those moved to DR-TB treatment cohort). Treatment outcomes are defined by the time of initiation on treatment; e.g., "2018 cohort successfully treated" reflect those who were initiated on treatment in 2018, even though treatment may have extended into 2019. For this reason, reports of treatment outcome data lag by one year. This indicator is a subset of the data reported in the core indicator "Treatment success rate." Calculation: (Numerator/Denominator) x 100	Number of children and adolescents (0–14) with new and relapse TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary), who were registered in a specified period that were cured or completed treatment	Number of children and adolescents (0–14) with new and relapse TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary) who initiated treatment in the same period.	Sex
Treatment success rate among PLHIV	**National Level**	Percent of people living with HIV (PLHIV) with new and relapse TB among PLHIV (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary) who were notified in a specified period that were cured or treatment completed, among the total number of people with new and relapse TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary) who were initiated on treatment during the same reporting period (excluding those moved to RR-TB treatment cohort). Treatment outcomes are defined by the time of initiation on treatment; e.g., "2018 cases successfully treated" reflect those who were initiated on treatment in 2018, even though treatment may have extended into 2019. For this reason, reports of treatment outcome data lag by one year. Calculation: (Numerator/Denominator) x 100	Number of PLHIV with new and relapse TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary), who were registered in a specified period that were cured or treatment completed	Number of PLHIV with new and relapse TB (bacteriologically confirmed or clinically diagnosed, pulmonary or extrapulmonary) who initiated treatment in the same period	Age (<15, 15+), sex
DS-TB treatment initiations	**National Level**	Number of people with laboratory-confirmed or clinically diagnosed DS-TB who initiated treatment for DS-TB during the reporting period.	Number of people with laboratory-confirmed or clinically diagnosed DS-TB who initiated treatment for DS-TB during the reporting period	N/A	Age (<15, 15+), sex, HIV status, public
Number of TPT initiations among contacts <5	**National Level**	Number of household contacts under 5 years old of bacteriologically confirmed pulmonary new and relapse TB cases notified in the reporting period who were started on TB preventive treatment (TPT).	Number of household contacts under 5 years old of bacteriologically confirmed pulmonary new and relapse TB cases notified in the reporting period who were started on TPT.	N/A	Sex

Indicator Name	PBMEF Level	Definition	Numerator	Denominator	Dis-aggregation
Number of TPT initiations among PLHIV	**National Level**	Number of PLHIV who were started on TPT during the reporting period.	Number of PLHIV who were started on TPT during the reporting period.	N/A	Age (0–4, 5–14, 15+), sex
CQI programs in place	**National Level**	Existence of a continuous quality improvement (CQI) platform(s) at all levels of the health system for 1) TB clinical care, 2) TB laboratory, 3) TB commodities, and 4) other whereby TB service delivery and relevant data and indicators are systematically monitored, their quality assessed, and decisions are made to address any operational problems or challenges identified.	Existence of a continuous quality improvement (CQI) platform(s) at all levels of the health system for the following: -TB clinical care CQI program? Yes/No -TB laboratory CQI program? Yes/No -TB commodities CQI program? Yes/No -Other CQI? Yes/No (if yes, please describe)	N/A	N/A
TB drugs meeting international minimum quality standards	**National Level**	Percent of anti-TB drugs procured locally or internationally which meet international minimum quality standards within a country. "International minimum quality standards" are defined and documented in the batch certificate. Standards and the reference organizations considered to be acceptable include WHO Prequalification of Medicines Programme (PQP)/ stringent regulatory authorities (SRAs)/ Expert Review Panel (ERP). Calculation: (Numerator/Denominator) x 100	Number of batches of anti-TB drugs procured locally or internationally for which a batch certificate showed acceptable results during the reporting period	Number of batches received of anti-TB drugs (procured during the reporting period)	N/A

Annex 1: WHO-recommended tests for diagnosis of TB drug resistance

	WRD	Drug resistance	Technology	Manufacturer
1	**Initial tests for diagnosis of TB with drug-resistance detection**			
1.1	Xpert MTB/RIF Ultra and Xpert MTB/RIF	RIF	Low complexity NAAT mWRD	(Cepheid, Sunnyvale, United States of America [USA]),
1.2	Truenat MTB, MTB Plus and MTB-RIF Dx tests	RIF		(Molbio Diagnostics, Goa, India)
1.3	Abbott Real Time MTB and MTB RIF/INH assays	RIF and INH	Automated moderate complexity NAATs	(Abbott Laboratories, Abbott Park, USA),
1.4	BD MAX MDR-TB assay	RIF and INH		(Becton, Dickinson and Company, Franklin Lakes, USA),
1.5	Hain FluoroType MTBDR assay	RIF and INH		(Bruker/Hain Lifescience, Nehren, Germany),
1.6	Roche cobas MTB and MTB-RIF/INH assays	RIF and INH		(Hoffmann-La Roche, Basel, Switzerland).
2	**Initial tests for diagnosis of TB without drug-resistance detection**			

2.1	TB-LAMP (loop-mediated isothermal amplification)	NO	Low complexity NAAT mWRD	(Eiken Chemical, Tokyo, Japan).
2.2	(LF-LAM) test the lateral flow lipoarabinomannan assay	NO	biomarker-based assay	(Alere Determine TB LAM Ag, USA)
3	**Follow-on diagnostic tests after TB confirmation**			
3.1	Xpert MTB/XDR Assay	INH, FQs, ETO and SLI drugs	Low complexity automated NAAT	(Cepheid, Sunnyvale, USA).
3.2	First-line LPAs GenoType MTBDRplus	RIF and INH	Moderate complexity	Bruker/Hain Lifescience, Nehren, Germany;
3.3	Second line LPAs GenoType MTBDRsl	FQ and SLI	Moderate complexity	Bruker/ Hain Lifescience, Nehren, Germany);
3.4	Genoscholar PZA-TB II	PZA	high complexity reverse hybridization NAAT	[Nipro Corporation, Osaka, Japan]);
3.5	Deeplex® Myc-TB	RIF, INH, PZA, EMB, FQ, BDQ, LZD, CFZ, AMK and STR;	targeted NGS tests, which couple amplification of selected genes with NGS technology	[GenoScreen]
3.5	AmPORE TB [Oxford Nanopore Technologies]; and	RIF, INH, FQ, LZD, AMK and STR		[Oxford Nanopore Technologies]
	TBseq®.	EMB		[ShengTing Biotech]

Annex 2: TB and Co-morbidities

Table. Overview of priority mental health conditions

Adapted from WHO mhGAP *Intervention Guide 2.0 (32)*	
• These common presentations indicate the need for assessment by persons trained in assessment, management and follow-up of these conditions, such as health workers trained in mhGAP. • If people present with features of more than one condition, then all relevant conditions need to be assessed. • All conditions apply to all ages, unless otherwise specified. • For emergency presentations (such as, but not limited to: imminent risk of self-harm/suicide, agitated or aggressive behaviour, acute alcohol intoxication), see page 18: Emergency Presentations of Priority Mental, Neurological and Substance Use Conditions in WHO *mhGAP Intervention Guide 2.0 (32).* • For full mental health assessment, management and follow up protocols, see WHO *mhGAP Intervention Guide 2.0 (32).* • For potential drug-drug interactions between mental health and TB treatment, see WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38).*	
Common presentation	**Priority condition**
• Multiple persistent physical symptoms with no clear cause • Low energy, fatigue, sleep problems • Persistent sadness or depressed mood, anxiety • Loss of interest or pleasure in activities that are normally pleasurable	**Depression**
• Multiple persistent physical symptoms with no clear cause • Persistent and excessive anxiety or worry • Muscle tension • Difficulty controlling worries • Difficulty concentrating and making decisions	**Anxiety**[a]
• Marked behavioural changes; neglecting usual responsibilities related to work, school, domestic or social activities • Agitated, aggressive behaviour, decreased or increased activity • Fixed false beliefs not shared by others in the person's culture • Hearing voices or seeing things that are not there • Lack of realization that one is having mental health problems	**Psychoses**

Annex 3: Tuberculosis Treatment Facility Card- TB 01

National TB Control Program Pakistan

Tuberculosis Treatment Facility Card **TB 01 (Front Side)**

TB. Registration No.										-		-							

BMU Name: _____ TB Care Facilitator Name: _____

Patient Name: _____

Father / Husband Name: _____

SEX M ☐ F ☐	**DOB**	**Age**
Date of Registration	/ /	

Patient Address _____

Occupation _____Phone no 1: _____

Phone No. 2: _____

Treatment Supporter Name: _____

Treatment supporter type / contact number			
Family	Community	LHW	Cell number

PATIENT IS REFERRED BY							
Self	CW	LHW	PB- HF	PVT-HF	Pharmacy	Camp	Other

CW; community worker, LHW; lady health worker, PB-Public, PVT-Private

RISK FACTORS	**Yes/No/Unknown**
HIV Infection / AIDS	Reg#._____
Contact of B+ PTB cases	Reg#._____
Diabetes	
Malnutrition	
Smoking	
Pregnancy	
Lactation	
Health care worker	
Other specify	

INVESTIGATIONS							
M	**Date**	**Examination Type**	**Lab No**	**Result**	**CXR**	**Weight (KG)**	Height (cm)
0		AFB Sm					
		Xpert					
		HIV					
		Other (Culture)					
2		AFB Sm					
		Other (Culture/Xpert)					
5		AFB Sm					
		Other (Culture/Xpert)					
6		AFB Sm					
		Other (Culture/Xpert)					

Sm: *Smear , X: Xpert , CXR- Chest X-ray, M-month of treatment*
Use blank column to enter results of other test done (as per required)

CNIC No. Patient ☐ Family member if <18 yrs) ☐

M. Tuberculosis DST Result*

	Date tested	Lab no	Results
RIFAMPICIN			
ISONIAZID			
Fluoroquinolone			

*Enter Results: R=resistant , S=Susceptible and NA =if not done, FQ – fluoroquinolone

DISEASE SITE:

Pulmonary ☐ Extra Pulmonary ☐

If EPTB Specify site

Pleura	Lymph node	Abdomen/ Peritoneum	Bone / joint	Menin ges	Other

Evidence of EPTB diagnosis (other than bacteriology)

Histology	X-Ray	U/Sound	MRI	Other

TYPE OF PATIENT (Based on TB Treatment History)

NEW	☐	Unknown previous treatment	☐
Re-Registered Case	*If re-registered case tick appropriate box below*		
Recurrent Case (Relapse)	☐	Treatment after Failure	☐
After loss to follow up	☐	Other previously treated	☐
Bacteriology confirmed "B+"	☐	**Clinically diagnosed**	☐

B+ are positive on AFB smear and/or Xpert(MTB) and/or culture

Treatment Regimen

Initial Phase

Regimen Type	**Drug Regimen (Initial Phase)**	**Tablets for Initial Phase**
Regimen-1 a (Adult)	2HRZE**(75/150/400/275)**	
Regimen-2 (Child)	2HRZ+E **(50/75/150)+100**	
Regimen-3*: (Adult)-HrTB	2HRZE+Lfx **(75/150/400/275) +250**	
Regimen-1 b (Adult) ****	2HRZE **(75/150/400/275)**	

only for TB cases who are laboratory confirmed Rifampicin sensitive, INH-Resistant and FQ-susceptible/Status unknown
****only for TB cases who are laboratory confirmed Rifampicin sensitive, INH-Resistant and FQ-Resistant***

National TB Control Program Pakistan **TB 01 (Back Side)**

Continuation Phase:

Regimen Type	Drug Regimen (Cont. Phase)	Tablets
Regimen-1 a (Adult)	4HR **(75/150)**	
Regimen-2 (Child)	4HR **(50/75)**	
Regimen-3: (Adult)-HrTB	4HRZE+Lfx **(75/150/400/275) +250**	
Regimen-1 b (Adult)	4HRZE **(75/150/400/275)**	

Drug Dosage – Separate Combination					
Name of ATT Drug	INH (100mg)	INH (300mg)	E (100mg)	E (400mg)	Z (400mg)
Dose/ No. of tablets					
Name of ATT Drug	Lfx (250mg)	Rifampicin (300 mg)	Rifampicin (450 mg)	Rifapentine/INH (300/300)	Rifapentine/ INH (150/150)
Dose/ No. of tablets					

APPOINTMENTS FOR DRUG COLLECTION & FOLLOW UP					
	Date Patients visited	**Weight (kg)**	**Next appointment date**	**Dose /Tablets**	**Remark (General Condition/Adverse Event)**
1					
2					
3					
4					
5					

TREATMENT OUTCOME	**Date :**	
☐ **Cured**	☐ **Treatment completed**	☐ **Died**
☐ **Treatment Failure**	☐ **Lost to follow up**	☐ **Not evaluated**
☐ **Re-enrolled on HrTB (Regimen3)***	☐ **Transferred /moved to DRTB register (DR TB No._____**	

Comments: _____

- **Declare Outcome if patient is Re-enrolled on HrTB (Regimen-3)**

TB/HIV Activities

TB patients tested for HIV at TB center		HIV Test Result .		Referred for Confirmatory testing of HIV to HIV center		TB Patients confirmed positive for HIV		ART Center Registration number (PLHIV Number)	HIV PositiveTB Patients put on ART	
Yes	No	Reactive	Non - Reactive	Yes	No	Yes	NO		YES	NO

CONTACT SCREENING : Household Contacts

Name of Contact		Relation	Age	SEX	Weight	Medical History [a]	Symptomatic [b]	Date & Result of Screening				TB	If not TB			Outcome of TPT ©	Identifier Code	Adverse Event / Comment
												Y/N						
							(Y/N)	Date	CXR	Xpert	Sm	P/EP.	TPT				(If TB, Reg No. if TPT, Reg No.)	
													H	HP	HR			
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		

a: 1.Chronic Liver disease, 2. History of Adverse Drug Reaction (ADR) to Isoniazid (INH)

b: 1.Cough (any duration), 2. Fever, 3.Weight loss, 4.Fatigue / Chest Pain, 5. Night Sweat, 6.Pregnant, 7.HIV, 8. Others

c : TC = Treatment Completed , LTFP = Lost to follow up , Ref = Refused , Died

Note: If the person have any medical history then don't proceed for TPT

National Tuberculosis Control Program Pakistan

TB PATIENT CARD (TB 02)

Registration No.										-		-					
CNIC						-							-				

Name _____

Address _____ Date of registration _____

Sex: M ☐ F ☐ Age ____ Date of treatment start _____

Name of TB Care Facility (BMU) _____

Phone No. _____

Disease site (tick one)

☐ Pulmonary ☐ Extra-Pulmonary specify

☐ Bac Confirmed ☐ Clinically Diagnosed

Type of patient (tick one)

☐ New

☐ Patient with unknown previous TB treatment history

☐ Recurrent Case

☐ Treatment after failure

☐ Treatment after Lost to Follow-up

☐ Other Previously treated patient

Treatment Outcome

Date of decision _____

☐ Cured ☐ Treatment completed

☐ Died ☐ Treatment failure

☐ Lost to follow up ☐ Not Evaluated

مریض کیلئے ضروری ہدایات

۱۔ یہ ایک بہت اہم کارڈ ہے اس کو اپنے پاس حفاظت سے رکھیں۔
۲۔ ڈاکٹر سے ملاقات، دوا کے حصول اور بلغم کا معائنہ کروانے کے لیے یہ کارڈ اپنے ہمراہ لائیں۔
۳۔ ٹی بی قابل علاج مرض ہے۔ ۴۔ کامیاب علاج کے لیے اپنے ڈاکٹر کی ہدایات پر عمل کریں۔
۵۔ کامیاب علاج کے لیے باقاعدگی سے دوا کھانا ضروری ہے۔
۶۔ اپنے گھر سے نزدیکی مرکز صحت سے ٹی بی کی دوا مفت حاصل کرنے کا فائدہ اٹھائیے۔
۷۔ مقررہ تاریخ پر مرکز صحت پر ضرور تشریف لائیے۔
۸۔ اگر آپ اپنے علاج میں تعاون کریں گے تو انشاءاللہ آپ مکمل طور پر صحت یاب ہو جائیں گے۔

بلغم کا معائنہ کرانے کی تاریخ

تاریخ	بلغم کا معائنہ کرانے کا مقام

نتیجہ علاج		علاج روکنے کی تاریخ	

TB TREATMENT - INITIAL PHASE			
RegimenType	**Drug Regimen**	**Dosage**	**Tablets**
Regimen-1a(Adult)	2HRZE	(75/150/400/275)	
Regimen-2(Child)	2HRZ+E	(50/75/150)+100	
Regimen 3 (Adult)	2HRZE + LFX	(75/150/400/275)+250	
Regimen 1b (Adult)	2HRZE	(75/150/400/275)	
**only for laboratory confirmed TB cases who are rifampicin sensitive, INH-Resistant and FQ-susceptible/ Status unknown*			

Current	No. of Tablets	Next	Current	No. of Tablets	Next

Date of Appointment of Drugs Collection

Appointment for follow up (Type of test)

Date	Clinical Examination

Remarks_____

National Tuberculosis Control Program Pakistan

TB TREATMENT - CONTINUATION PHASE			
Regimen	**Drug Regimen**	**Dosage**	**Tablets**
Regimen 1 a (Adult)	4HR**	(75/150)	
Regimen 2 (Child)	4HR**	(50/75)	
Regimen 3* (Adult)	4HRZE + LFX	(75/150/400/275)+250	
Regimen 1b (Adult)**	4HRZE	(75/150/400/275)	

INVESTIGATIONS

M	Date	Bacteriological Examination	Lab No	Result	CXR	Weight (KG)	Height (cm)
0		AFB Smear					
		Xpert					
		HIV					
		Other (Culture)					
2		AFB Smear					
		Other (Culture/Xpert)					
5		AFB Smear					
		Other (Culture/Xpert)					
6		AFB Smear					
		Other (Culture/Xpert)					

***only for TB cases who are laboratory confirmed Rifampicin sensitive, INH-Resistant and FQ-Resistant*

National TB Control Program Pakistan

(TB 03)

TB CARE FACILITY (BMU) / DISTRICT TB REGISTER

Province Code: _____ District Code: _____ Facility Code: _____

Instructions

Smear results reported as follows:

Grading - ZN Microscopy

No. of AFB Observed	Report
No AFB in 100 fields	*Negative*
1-9 AFB in 100 fields	*Record exact number of bacilli*
10-99 AFB in 100 fields	*1+*
1-10 AFB/fields in 50 fields	*2+*
More than 10 AFB/field in 20 field	*3+*

Grading - FM Microscopy

200X	400X	Report
No AFB in one length	No AFB in one length	Negative
1-4 AFB in one length	1-2 AFB in one length	Confirmation required*
5-49 AFB in one length	3-24 AFB in one length	Scanty (exact number)
3-24 AFB in one fields	1-6 AFB in one fields	1+
25-250 AFB in one fields	7-60 AFB in one fields	2+
>250 AFB in one fields	>60 AFB in one fields	3+

* Confirmation required by another technician or prepareanother smear, stain and read.

Xpert MTB/Rif test result reported as follows:

"MTB" Column; *Det=MTB Detected*
ND=MTB Not Detected
INV=Invalid/Error/No Result

"RR" Column *Det=Rifampicin Resistance Detected*
ND=Rifampicin Resistance Not Detected
IND=Rifampicin Resistance Indeterminate

Disease type
NEW: No previous history of ATT
Re-registered Cases
RLP : Recurrent
TAF : Treatment after failure
L2FUP : Lost to follow up
H/O – History of
ATT –Anti TB treatment
UK : Unknown

Treatment outcome

C= CURED
TC=Treatment completed
D=Died
F- Failure
NE= Not evaluated
LTFUP= Lost to follow up

HIV Status
R – Reactive
NR – Non- Reactive
UK : Unknown

Initial Phase / Continuation Phase

Regimen Type	Drug Regimen (Initial Phase)	Drug Regimen (Cont. Phase)
Regimen-1a (Adult)	2HRZE **(75/150/400/275)**	4HR **(75/150)**
Regimen-2 (Child)	2HRZ+E **(50/75/150) +100**	4HR **(50/75)**
Regimen-3: (Adult)-HrTB	2HRZE+Lfx **(75/150/400/275) +250**	4HRZE+Lfx **(75/150/400/275) +250**
Regimen-1b (Adult)	2HRZE **(75/150/400/275)**	4HRZE **(75/150/400/275)**

TB CARE FACILITY (BMU) / DISTRICT TB REGISTER **TB-03**

Date of Registration												
TB Registration no.												
Patient name												
Father / husband name												
Gender M/F												
Age												
CNIC												
Address												
Contact #												
Date Treatment Started												
Site PTB / EPTB												
NEW												
Re-registered Cases	Recurrent (Relapse)											
	Treatment After Failure											
	Treatment After lost To Follow Up											
	Other											
H/O ATT Unknown												
Transfer In												
Investigations "0" Month	HIV Test Result (R / NR / UK)											
	AFB sm											
	Xpert	MTB										
		RR										
	CXR											
	Remarks/any other investigation											

TB CARE FACILITY (BMU) / DISTRICT TB REGISTER TB-03

Regimen 1,2,3	Follow up Smear results: 2M AFB sm (Result / Lab No./Date)	Follow up Smear results: 5M AFB sm (Result / Lab No./Date)	Follow up Smear results: 6M AFB sm (Result / Lab No./Date)	Other Test	DST - Result: R (Result / Lab No./Date)	DST - Result: H (Result / Lab No./Date)	DST - Result: FQ (Result / Lab No./Date)	End TreatmentDate	Outcome: Cured	Outcome: Treatment Completed	Outcome: Died	Outcome: Failure	Outcome: Lost to follow up	Outcome: Not Evaluated	Re-enrolled on HrTB Regimen	Moved to second line treatment register (Date)	Contact Tracing HH: No. ofHH Contact 0-4	No. ofHH Contact 5-14	No. ofHH Contact 15+	No. of Contacts Screened 0-4	No. of Contacts Screened 5-14	No. of Contacts Screened 15+	No. of ConfirmedTB Cases Detected 0-4	No. of ConfirmedTB Cases Detected 5-14	No. of ConfirmedTB Cases Detected 15+	No. of Contacts put on preventive Treatment 0-4	No. of Contacts put on preventive Treatment 5-14	No. of Contacts put on preventive Treatment 15+	Remarks (e.g. Adverse events, Referring Facility)

Annex 6: TB Laboratory Register TB04

TB 04

National TB Control Program

(TB LABORATORY REGISTER)

National TB Control Program Pakistan

Instructions

a. For diagnostic testing employing serial sputa this is the date of receipt of the first specimen.
b. Y= Yes; N=No; Unk=Unknown
c. Y=Previously Treated; N= Not previously treated; Unk= unknown
d. Patient on TB treatment; indicate month of treatment at which follow-up examination is performed.
e. Smear results reported as follows:

Grading - ZN Microscopy

No. of AFB Observed	Report
No AFB in 100 fields	Negative
1-9 AFB in 100 fields	Record exact number of bacilli
10-99 AFB in 100 fields	1+
1-10 AFB/field in 50 fields	2+
More than 10 AFB/field in 20 field	3+

exact number)

Grading - FM Microscopy

200X	400X	Report
No AFB in one length	No AFB in one length	Negative
1-4 AFB in one length	1-2 AFB in one length	Confirmation required*
5-49 AFB in one length	3-24 AFB in one length	Scanty (exact number)
3-24 AFB in one field	1-6 AFB in one field	1+
25-250 AFB in one field	7-60 AFB in one field	2+
>250 AFB in one field	>60 AFB in one field	3+

*confirmation required by another technician or prepare another smear, stain and read.

Xpert MTB/Rif test result reported as follows:

f "MTB" Colum; Det=MTB Detected;
Det (T) =MTB Detected Trace
ND=MTB Not Detected
INV=Invalid/Error/No Result

g "RR Colum; Det=Rifampicin Resistance Detected;
ND=Rifampicin Resistance Not Detected;
IND=Rifampicin Resistance Indeterminate

National TB Control Program Pakistan — Laboratory Register for Smear Microscopy and Xpert MTB/RIF — (TB04)

Lab. Serial No	Date Specimen Received	Patient Name	Sex M/F	Age (Date of Birth)	Patient Address/ Contact #	Patient NIC #	Referred by (Health Facility)	HIV Infection (Y/N/Unk)	Patient Previously treated for TB (Y/N/Unk)	Examination Type		Examination Result				BMU and TB Register No.	Remarks
										Diagnosis	FUP	Smear Microscopy		Xpert			
												1	2	MTB	RR		
											Month	Date	Date	Date			

Annex 7: Laboratory Request form TB05

TB LABORATORY REQUEST FORM (TB05)

XPERT MTB/RIF AND/OR AFB MICROSCOPY TESTING FOR TB DIAGNOSIS

PATIENT IDENTIFICATION (ID): **Patient CNIC #:**☐☐☐☐☐-☐☐☐☐☐☐☐-☐

Name of Patient: _____Age_____ (yrs): Sex: M /F_____

Address: _____City _____District_____ Contact #: _____

Referring Health Facility Name: ----------☐OPD/ ☐ "In-Patient" Ward# --------Bed# ----------

Name of Physician: _____Designation: _____Contact#_____Email:_____

Reason for Laboratory request	☐ **Diagnosis**	☐ **Follow-up - If yes**	**F-up Month**_____	**TB Reg#:**
Clinical history				
Disease site	☐ Pulmonary	☐ Extrapulmonary	If Extra pulmonary specify	
HIV +ve	☐ YES	☐ NO	☐ Unknown	
Previous TB treatment	☐ YES	☐ NO	☐ Unknown	
Contact of B+ve TB Patient	☐ YES	☐ NO	☐ Unknown	
Previous Laboratory results				
AFB microscopy	☐ Yes ☐ No	Date	☐ Positive	☐ Negative
Xpert MTB/RIF	☐ Yes ☐ No	Date	MTB-	RR- _____
Laboratory Request				
Specimen Origin	☐ Pulmonary	☐ Extra Pulmonary If yes specify		
Specimen type:	☐ Sputum	☐ Gastric aspirate	☐ BAL	☐ Fluid _____
	☐ Tissue Biopsy	☐ FNA_____	☐ Pus_____	☐ other _____
Test request	☐ Xpert MTB/RIF		☐ AFB microscopy	

**Lymph node, pleura, Bone/ spine, Brian/meninges, kidney, Pericardium/heart*

Date specimen collected: : ____/_____/20_____

Date (If) specimen sent to Xpert Testing laboratory ☐ through courier or ☐ Other mean) : ____/_____/20_____

LABORATORY REPORT: & XPERT MTB/RIF ASSAY & AFB MICROSCOPY *(To be completed in laboratory)*

Laboratory Name: _____ **Laboratory Registration No:** _____

Patient CNIC #:☐☐☐☐☐-☐☐☐☐☐☐☐-☐

Name of Patient :_____(Yrs):_____ Sex: _____

Address: _____ _____District_____ _____Contact #: _____

Referring Health Facility Name: _____☐ OPD _____ ☐Ward/Bed# _____

Reason for Laboratory request : ☐ Diagnosis ☐ Follow-up - If yes F-up Month_____ **TB Reg#:**_____

Specimen collection date: ___/___/20_____ **Date specimen received** __/___/20_____

RESULT: **Date report**

Specimen:	**Gross Appearance:**			**Quantity**	
Test Results					
AFB smear	**Lab#**	☐ **Positive**	**Sm grade**		☐ **Negative**
MTB/RIF-ultra	Lab #	**MTB**	☐ **Detected**	☐ High ☐ Med ☐ Low ☐ V. Low ☐ Trace	
			☐ Not detected	☐ No results	
		Rifampicin Resistance	☐ Not detected	☐ **Detected**	☐ Indeterminate

Remarks: ----------

Report prepared by: **Name**_____ Signature_____

NATIONAL TB CONTROL PROGRAM PAKISTAN

(TB 07)

QUARTERLY REPORT ON TB CASES REGISTRATION

INDIVIDUAL / CONSOLIDATED (TICK ONE)

Revised 2024

National TB Control Program

QUARTERLY REPORT ON TB CASES REGISTRATION

INDIVIDUAL/CONSOLIDATED (TICK ONE)

Ministry of National Health Services Regulations & Coordination

TB-07

Name of TB Care Facility (BMU): _____ District: _____ Patients registered during: _____ Quarter of year: _____

Name of District TB Coordinator / Facility In charge: _____ Date of completion of this form: _____

All TB Cases Registered	New (N)	Recurrent cases(R)	Previous Treatment History Unknown (UK)	**New episode (N+R+ UK)**	**Re-registered Cases (Excluding Recurrent cases)**			Total
					Treatment after Failure	Treatment after lost to follow-up	Other	
Pulmonary, Bacteriologically Confirmed								
Pulmonary, Clinically Diagnosed								
EPTB -Bacteriologically confirmed								
EPTB- Clinical diagnosed								
Total								

Block 2: All New, Recurrent and Previous treatment history unknown Cases registered during the period by Age Group and Gender

	0-4		5-14		15-24		25-34		35-44		45-54		55-64		65 & above		Grand Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
Pulmonary, Bacteriologically Confirmed																	
Pulmonary, Clinically Diagnosed																	
EPTB -Bacteriologically confirmed																	
EPTB- Clinical diagnosed																	
Total																	

Block 3: Presumptive TB case Identification, Laboratory Diagnosis and use of WRD

Total New OPD in Quarter	No. of Presumptive TB Cases identified		No. of T B Presumptive tested using				Among Presumptive TB cases tested number reported B+				Among all registered number of B+ TB Cases	Among All (N+R+UK), number tested by Gene Xpert
	Total	Through Community Referrals (LHWs)	AFB	Xp & AFB	XP	G Total	AFB	AFB + Xpert	Xpert	G.Total		

Block 4: TB HIV Activities

No. of TB patients tested for HIV	HIV Reactive	TB Patients, confirmed positive for HIV	HIV-TB Patients put on ART

HIV patients tested for TB	HIV patients, confirmed for TB	TB-HIV patients put on TB Tx	HIV positive TB negative patients put on TPT			
				0-4	5-14	15 +
			6 H			
			3 HR			
			3 HP			

Block 5: Pulmonary Bacteriologically Confirmed TB Cases / Extra Pulmonary TB cases with DST Result

Sensitive = S Resistance =R	**PTB**						**EPTB**					
	Rifampicin		**Isoniazid**		**Fluoroquinolone**		**Rifampicin**		**Isoniazid**		**Fluoroquinolone**	
	S	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**
New + UK												
Recurrent												
Re-registered												
Total												

Block 6 : Contact Tracing HH

Total No. of HH of B+ PTB			No. of HH contacts of B+ PTB Cases screened			No. of TB Cases diagnosed Among HH contact screened			No. of HH contacts initiated on TPT				HIV negative Immuno-compromised on TPT		
0-4	5-14	15+	0-4	5-14	15+	0-4	5-14	15+		0-4	5-14	15+	0-4	5-14	15+
									6 H						
									3 HR						
									3 HP						

Block 7 - Stock position Anti-TB Drugs & Diagnostics **Name of Facility _____** **Quarter _____**

	Name of ATT Drug	Opening Balance	Qty. Received From NTP	Qty. Received From Domestic Resource (Province / Region)	Utilized / Dispensed	Return to Districts / Store	Positive adjustment	Expired/ Discarded	Closing Balance	Any Short Expiry within 3-Months	Stock Out in Review Quarter Yes/No	If "Yes" Then Number of days of stock
Adults	RHZE (150,75,400,275)											
	RH (150,75)											
	Rifampicin (300 mg)											
	INH (300mg)											
	Z (400mg)											
	E (400mg)											
	Lfx (250mg)											
Peads	RHZ (50,75,150)											
	RH (50,75)											
	INH (100mg)											
	E (100mg)											
TPT Adults	Rifapentine /INH (300/300)											
TPT Peads	INH (100)											
Xpert	MTB/RIF											
HIV	Alere Combo (T1)											

NATIONAL TB CONTROL PROGRAM PAKISTAN

(TB 09)

QUARTERLY REPORT ON TREATMENT OUTCOMES

INDIVIDUAL BMU / CONSOLIDATED (TICK ONE)

Updated - 2024

TB-09

National TB Control Program

QUARTERLY REPORT ON TREATMENT OUTCOMESINDIVIDUAL BMU / CONSOLIDATED (TICK ONE)

Name of TB Care Facility (BMU): _____ District: _____	Patients registered during: _____ Quarter of year: _____
Name of TB Coordinator/Facility incharge: _____	Date of completion of this form: _____
Signature: _____	

Block-1: All TB cases registered during the quarter

TB Patient Type		Number ofTB Cases registered	TREATMENT OUTCOMES												Initiated on HrTB (Regimen-3) (Y)		Moved/ Transferred to the DR-TB register at the time of diagnosis (Z)		Total Evaluated (X-Y-Z)
			Cured		Treatment completed		Treatment failed		Died		Loss to follow-up		Not evaluated						
	Age / Gender	(X)	<15	>=15	<15	>=15	<15	>=15	<15	>=15	<15	>=15	<15	>=15	<15	>=15	<15	>=15	
A. Pulmonary TB Bacteriologically confirmed (N+R+UK)	Male																		
	Female																		
B. Pulmonary TB Clinically Diagnosed (N+R+UK)	Male																		
	Female																		
C. Extra Pulmonary TB case (N+R+UK)	Male																		
	Female																		
Treatment outcome of subset of patients																			
Enrolled/Re-enrolled on HrTB (Regimen3)																			
A-1: HIV - Positive PTB and EPTB (N+R+UK)																			
D. Re-registered Cases (Excluding Recurrent cases)																			

Block 2: Bacteriologically Confirmed TB Cases with DST Result							Block 3: No. of Patient Put On Each Treatment Regimen				Block 4: No. of Patient Put On Preventive Treatment Regimen						
	Rifampicin		Isoniazid		Fluoroquinolone			Regimen 1:	Regimen 2:	Regimen 3:	Regimen	Total	Completed	Lost to follow up	Died	Refused	Put on ATT
	Sens	Resist	Sens	Resist	Sens	Resist		2HRZE / 4HR	2HRZ+E / 4HR	6HRZE + LFX	6H						
New + UK							New +UK				3HR						
Recurrent cases							Recurrent cases				3HP						
Re-registered							Re-registered				Total						

Annex 10: Pre-Registration Referral /Transferred out Form TB10

PRE-REGISTRATION REFERRAL / TRANSFERRED OUT FORM TB-10

Reason for Referral (Tick appropriate box)

☐ Pre-registration referral ☐ Transferred out ☐ Refer to PMDT site

Name of Patient _____ Age_____ Gender _____

CNIC # _____ Mobile number _____

Patient address _____

Type of patient:

☐ PTB ☐ EPTB ☐ New ☐ Recurrent cases ☐ Re-registered TB cases

TB registrations Number _____ Date of Treatment Started _____

Regimen (1,2,3,RRTB) _____ X-Ray _____

Additional Information _____

Laboratory Result:

Xpert _____ MTB _____ Rif _____

AFB Microscopy _____

Document Attached:

☐ TB-01 ☐ TB-05 Any other _____

	Referring Facility	Receiving Facility
Date referred / received		
Signature		
Name of health staff		
Designation		
Facility name		
District		
Province		
Contact Number		
Email		
Pre-Registration Referral is the process of moving a TB patient prior to registration in a TB Care Facility (TB 03) for the purpose of start of treatment. In case of pre-registration referral the outcome will be declared by the receiving unit.		
Transfer Out TB Patient A TB Patient registered in a TB care facility (TB 03) to continue his same treatment in another TB care facility with a different TB(03) register but with the same registration number.		

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