

National Guidelines

for the Control of
Tuberculosis in Pakistan

Revised

2019



National TB Control Program

National Tuberculosis Control Program
Ministry of National Health Services, Regulation & Coordination
Government of Pakistan
www.ntp.gov.pk



Government of Pakistan



**NATIONAL TUBERCULOSIS CONTROL
PROGRAMME PAKISTAN**

National TB Guidelines

**Revised & Updated
2019**

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Executive Summary

The purpose of these guidelines is to familiarize the readers with TB control Programme components and standardized protocols for diagnosing and successfully treating sensitive and drug resistant tuberculosis patients. The guidelines are intended to be a reference document for all those who are involved in TB control activities in Pakistan.

Prompt, accurate diagnosis and effective treatment are not only essential for good patient care but also key elements in the public health response to tuberculosis and are the cornerstone of tuberculosis control. Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are performing an important public health function that entails a high level of responsibility and individual patient and community is the main stakeholder.

National Guidelines have incorporated the most up-dated WHO definitions and diagnostic treatment protocols and also other literature related to TB control in programmatic context to address sensitive and drug resistant TB in country situation and setting. It has been prepared in line with 'International Standards' for Tuberculosis Care'. These 'Standards' intended to facilitate the effective engagement of all care providers in delivering high-quality care for patients of all ages, including those with sputum smear-positive, sputum smear-negative, and extra pulmonary tuberculosis, tuberculosis caused by drug-resistant mycobacterium tuberculosis complex (*M. tuberculosis*) organisms, and tuberculosis combined with human immunodeficiency virus (HIV) infection.

National Guidelines has been organized to address all the essential TB control programme components. The guideline provides a most up-date information of TB epidemiology in Pakistan and strategies to control the disease in coming years. In addition to new definitions and concepts of TB control (passive and active), 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 control programme management, capacity building, infection control, monitoring and evaluation.

Abbreviations

ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
ART	Anti Retroviral Treatment
ATT	Anti Tuberculosis Treatment
B+	Bacteriologically Positive
BHU	Basic Health Unit
CHTB	Child hood TB
CHW	Community Health Worker
CPT	Co-trimoxazole Preventive Therapy
DHO	District Health Officer
DHQ	District Headquarter Hospital
DLS	District Laboratory Supervisor
DMU	Drug Management Unit
DO	Direct Observation
DOTS	Directly Observed Treatment (short Course)
DR TB	Drug Resistant TB
DRS	Drug Resistance Survey
DST	Drug Sensitivity Testing
DTC	District TB Coordinator
EDO	Executive District Officer
EPTB	Extra Pulmonary TB
EQA	External Quality Assurance
FLD	First Line Drug
FM	Fluorescent Microscopy
GDF	Global Drug Facility
GF	Global Fund
GNP	Gross National Product
GP	General Practitioner
HCP	Health Care Practitioner
HH Contacts	House Hold Contacts
HIV	Human Immunodeficiency Syndrome
HMIS	Health Management Information System
HPF	High-Power Field
HSS	Health System Strengthening
HTC	HIV testing counselling
IDPs	Internally Displaced Persons
IEC	Information, Education and Communication
IGRAs	Interferon Gamma Release Assays
INH	Isoniazid
IPT	INH Prophylaxis Therapy

LED	Light-emitting Diode Microscope
LED	Light Emitting Diode
LHW	Lady Health Worker
LPA	Line Probe Assay
LTBI	Latent TB Infection
M&E	Monitoring and Evaluation
MDG	Millennium Development Goals
MDR-TB	Multi-Drug Resistant Tuberculosis
MO	Medical Officer
NGOs	Non-government Organizations
NSP	National Strategic Plan
NTP	National Tuberculosis Control Programme
PCS	Pakistan Chest Society
PDL	Prison DOTS linkages
PHC	Primary Health Care
PHPM	Pharmaceutical Health Product Management
PITC	Provider Initiated Testing & Counselling
PLHIV	People Living with HIV
PMA	Pakistan Medical Association
PMDT	Programmatic Management of Drug Resistant TB
PPD	Purified Protein Derivative
PPM	Public Private Mix
PRL	Provincial Reference Laboratory
PSCM	Procurement and Supply Chain Management
PTB	Pulmonary TB
PTCs	Presumptive of TB Cases
PTP	Provincial Tuberculosis Control Programme
RDTs	Rapid Diagnostic Tests
RHC	Rural Health Centre
RR-TB	Rifampicin-resistant TB
SLD	Second Line Drug
TB	Tuberculosis
TBC	Tuberculosis Clinic
TBIC	Tuberculosis Infection Control
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

Anti-tuberculosis drug abbreviations

Am	Amikacin
Am/Clv	Amoxicillin/ Clavulanate
Bdq	Bedaquiline
Amx/Clv	Amoxicillin/Clavulanate
Cfx	Ciprofloxacin
Cfz	Clofazimine
Clr	Clarithromycin
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delaminid
E	Ethambutol
Eto	Ethionamide
FQ	Fluoroquinolone
Gfx	Gatifloxacin
H	Isoniazid
Imp/Cln	Imepenem/Cilastatin
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
Ofx	Ofloxacin
PAS	Para-aminosalicylic acid
PAS-Na	Para-aminosalicylate sodium
Pto	Protionamide
R	Rifampicin
Rfb	Rifabutin
S	Streptomycin
Th	Thioacetazone
Trd	Terizidone
Vi	Viomycin
Z	Pyrazinamide

Foreword

National TB Control Program, working under the Ministry of National Health Services, Regulation and Coordination, Government of Pakistan adapts and implements World Health Organization recommended 'The End TB Strategy' for effective control of TB in Pakistan. The program envisages a TB free Pakistan by year 2035. The provision of free of cost quality TB care to all who need is the prime objective of National TB Control program.

National TB Control Program Pakistan in collaboration with its Provincial TB Control Programs and partners developed these guidelines in light of WHO recommendations in 2017. With these new recommendations WHO consolidated all aspects of TB treatment and Care into one document for the ease of its readers and implementers.

To keep abreast with these new recommendations Pakistan also revised its National TB treatment guidelines and the key areas covered include TB diagnosis, TB therapy for adults, adolescents and children including special populations. We have also added testing and treatment steps in tables and algorithms for ready reference of its users which can easily be printed into posters to be available in our treatment centers all over the country.

The target audience of these guidelines are health care professionals providing care and treatment to TB Patients including doctors, clinical officers, nurses, pharmacists, service providers, laboratory technologists and program management staff.

The development of this edition of the Guidelines has been done through extensive efforts put in by National & Provincial Technical team including WHO & partners. The process was led by National Technical team for TB treatment and conducted national consultations and getting feedback from experts and implementers and incorporating it into the document and then reviewing the final document word by word and page by page in a series of email correspondences.

We hope that this Guideline will improve the knowledge of its readers on the new recommendations on TB diagnosis, treatment and care and will help in rapid scale up of comprehensive and quality assured TB services to its clients in Pakistan.

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INTRODUCTION

Chapter-1 TB Epidemiology and TB Control in Pakistan

Country Overview

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

Pakistan is a federation that comprises four provinces: Punjab, Khyber Pakhtunkhwa (+ FATA), Sindh, and Balochistan and three territories: Islamabad Capital Territory, Gilgit-Baltistan, and Azad Jammu & Kashmir.

Pakistan is the world's sixth (1) most populous country with an estimated population of 207 million. In 2017, 6th Population and Housing Census were conducted by the Pakistan Bureau of Statistics, after 19 years. Punjab and Sindh are the most densely populated provinces of the country.

Province / Region	Capital	Population	
Punjab	Lahore	101,876,951	51.7%
Sindh	Karachi	47,886,051	22.5%
Khyber Pakhtunkhwa (+FATA)	Peshawar	32,901,665	16.7%
Balochistan	Quetta	11,426,926	5.8%
Gilgit-Baltistan	Gilgit	3,743,304	1.9%
Azad Jammu & Kashmir	Muzaffarabad	847,169	0.4%
Islamabad Capital Territory	Islamabad	1,851,950	0.9%



Pakistan is a low middle income country with nominal GDP per capita of \$1,516 (2). Total life expectancy at birth is 66.4 years and approximately 35% of the population is under 15 years of age (1). More than 60% of the total population lives in rural areas like other South Asian countries, health and sanitation infrastructure is adequate in urban areas but is generally poor in rural areas. Factors like poverty, malnutrition, poor housing and sanitation, inadequate health care facilities, population migration and urbanization, political instability and refugee are key challenges in health care in country.

Health Care System

Pakistan's health care delivery system includes provincial and district public health departments, other government sector organizations (including armed forces), non-governmental organizations (NGOs) and private sector with profit and not for profit service provision. An estimated two third of the population initially accesses health-care through private sector (3). Despite the significant role, the private sector is largely unregulated and functions predominantly for profit. The Federal Ministry of Health (MoH) was dissolved in June 2011 and the overall responsibility for health services was devolved to the provinces. Provincial healthcare Commissions are striving for developing and enforcing Minimum Service Delivery Standards (MSDS) to be implementing at all levels of healthcare. The public sector is the main source for the provision of preventive care and hospital care to the urban and rural population. Communicable diseases are still leading causes of morbidity and mortality and non-communicable diseases are on the rise.

TB CONTROL IN PAKISTAN

TB is one of the major public health problems in Pakistan, with the country ranking fifth among TB high-burden countries worldwide. The WHO-recommended DOTS strategy was piloted in 1995 in Pakistan. Major progress towards TB control, however, was achieved after the revival of the National TB Control Programme in 2001 when TB was declared a national public health emergency through the “Islamabad Declaration”. TB control Programme has treated nearly 4 million people with quality assured drugs since its revival while maintaining the treatment success rate of more than 90%. Although steady progress has been made from 2001 to improve case detection, TB continues to be a major public health problem.

TB CARE SERVICES in PAKISTAN

The following TB care diagnostic and treatment services are established across the country in public and private sector.

Table-1: Diagnostic and Treatment Services for TB

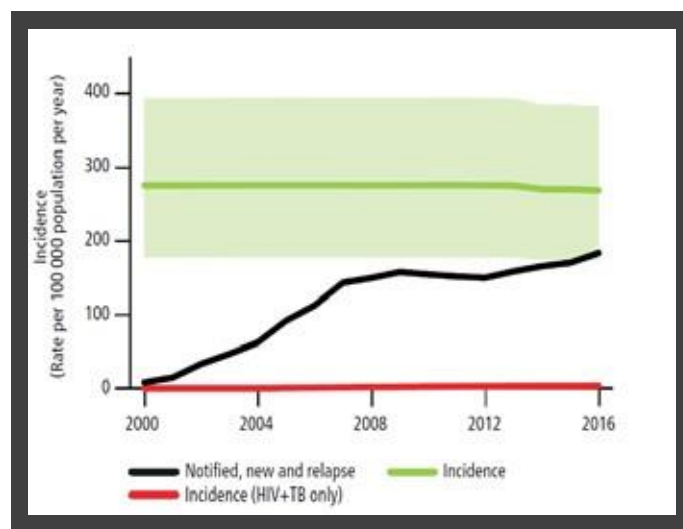
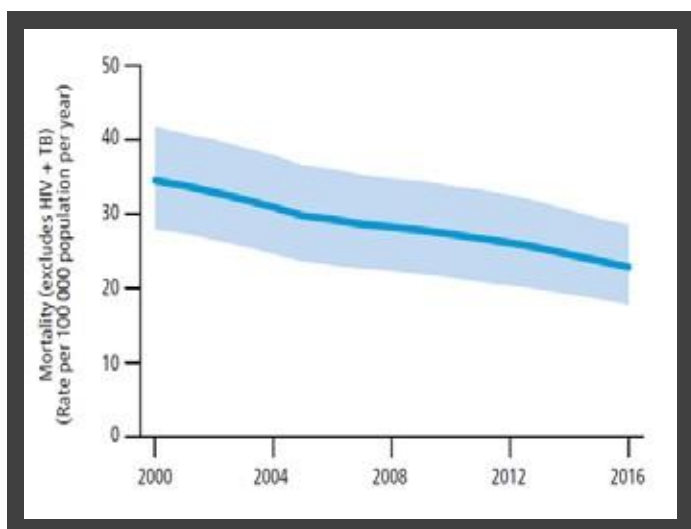
	Public	Private	TOTAL
Diagnostic Services			
Microscopy Laboratories	1,360	454	1,814
Xpert Testing	272	34	306
Culture services	18	04	22
Genotypic DST –(LPA)	05	02	07
Phenotypic DST	03	02	05
Digital X-Ray CAD4TB	09	52	61
Treatment Services			
Basic Management units + (PPM 2,3,4)	1,360		1,360
General Practitioner (PPM-1)		6,421	6,421
Programmatic Treatment sites	29	04	33
HIV surveillance sites	40		40

1.1 TB Epidemiology in Pakistan

Incidence and Prevalence

Pakistan ranks 5th among 30 high-burden countries for TB and 5th for Drug Resistant TB (DRTB). Disease burden is based on nationwide prevalence survey (2010-11) (4) and Drug resistance survey (2012-13) (5) a high tuberculosis (TB). Estimated TB incidence and prevalence is respectively 267 and 341/100K with an estimated 525,000 new TB cases each year. TB mortality is showing decline and currently is at 27 deaths per 100K population (2017) (6).

According to WHO global TB report 2018 (6), the incidence of TB in the general population is 267 per 100,000 populations. A significant decline is seen in TB mortality from 56 to 27/100K population but a very slow decline is noted in TB incidence over the years and with current pace it may take decades to control TB in the country.



Based on the estimated incidence of 267 per 100,000 populations, there were 525,000 incident TB cases in 2017 including 57,000 cases among less than 15 years.

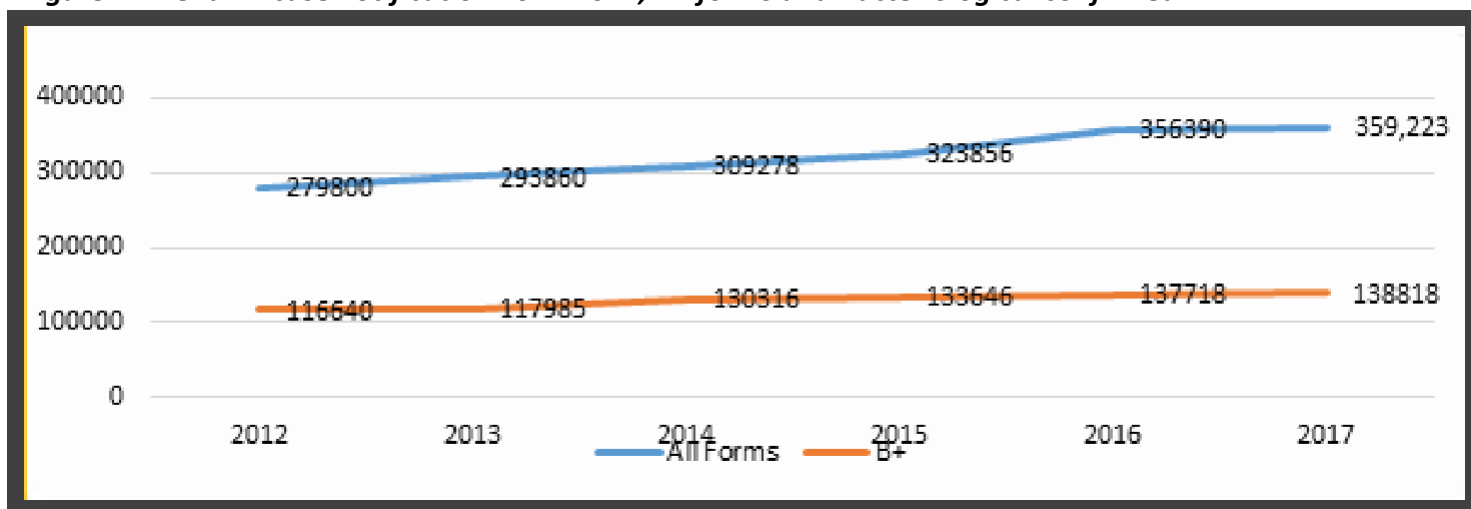
Table-2: Estimated TB incidence by age and sex 2017

	0-14 years	> 14 years	Total
Females	27,000	207,000	235,000
Males	30,000	261,000	291,000
Total	57,000	468,000	525,000

TB Case Notification

TB Control Programme notified 359,223 incident TB cases in 2017 which is 68% of the estimated cases. Among the notified cases, 80% are Pulmonary TB (PTB). Among PTB cases, 48% are bacteriologically confirmed.

Figure-1: Trend TB case notification 2012-2017; All forms and Bacteriological confirmed



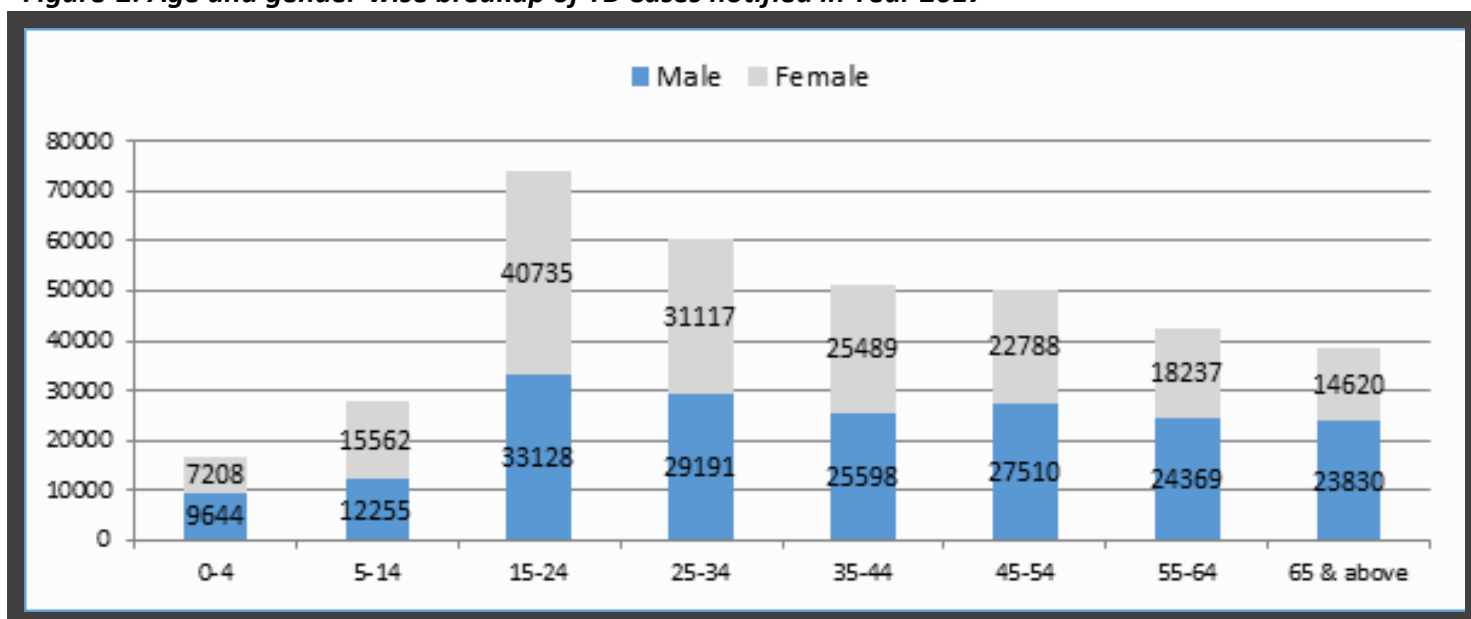
The detail of enrollment in 2017 is as below.

Table-3: National TB case notification trend by disease site and previous history of TB treatment

	New	Relapse	Unknown	Treatment after Failure	Treatment after loss to Follow-up	Other
PTB-B+	128,806	9,896	116	1,283	1,116	2,946
PTB-CD	145,942	3,503	116	124	453	2,944
EPTB	69,665	1,115	64	74	137	997
	344,413	14,514	296	1,481	1,706	6,887

Among the notified cases, 12% are pediatric cases. 51% of the patients are from economically productive age group (15-44 years). 11% are age 65 and above while 49% are females. The detail of age and gender-wise break up is as below:

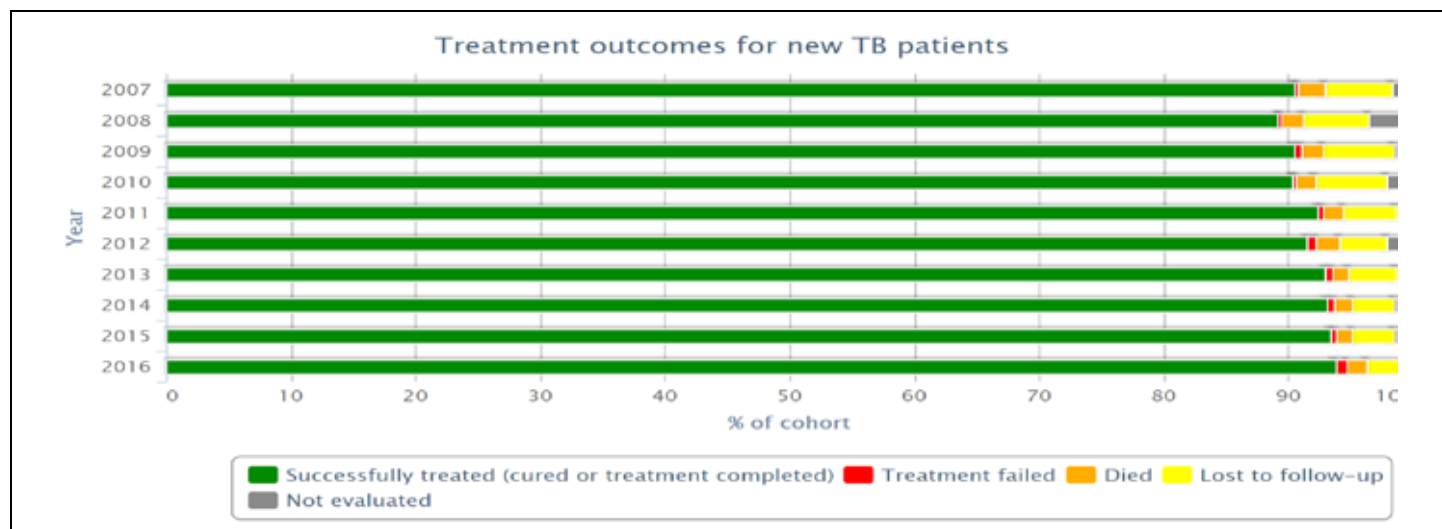
Figure-2: Age and gender-wise breakup of TB Cases notified in Year 2017



Treatment Outcomes

Since 2008, the Programme has successfully treated more than 90% TB cases. Below is the graph representing treatment success rate over the years:

Figure-3: Treatment Outcomes for new TB patients (2007-2016)



Contribution of the Private Sector

Most of the population has their first contact with a private provider for health care therefore, it is important to involve private practitioners in TB care services. Many private facilities, including solo private practitioners, private hospitals/clinics, NGOs, pharmacies, and informal practitioners are involved in the management of TB. Public-Private Mix (PPM) aims to establish linkages between private practitioners and the public sector to improve access and standardize TB care. In 2017, the contribution of the PPM is 30% (6).

TB Notification across provinces and regions

The province and region wise detail of notification and contribution of the public and private sector is as below:

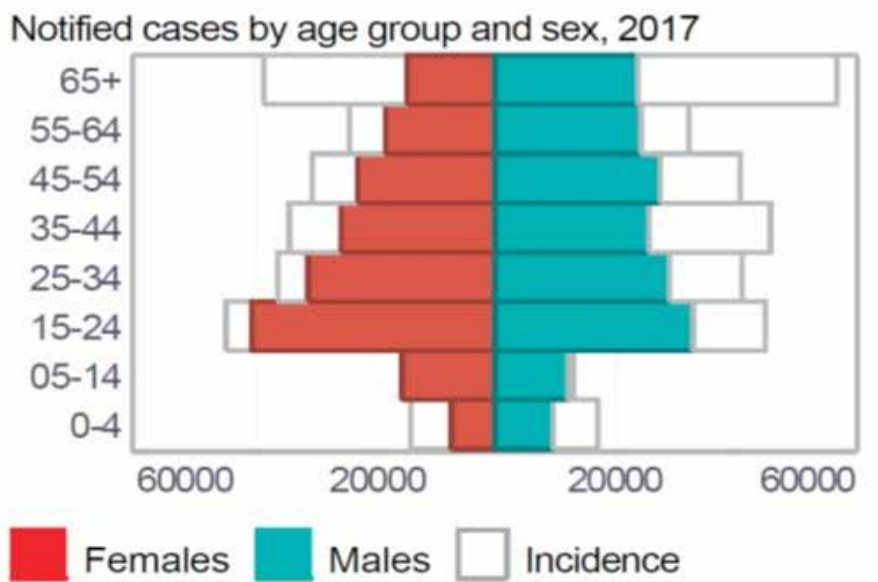
Table-4: Notification of TB cases by provinces and regions (Year 2017)

	Estimated cases	Notified cases	Public sector	Private sector	CDR	CNR	% Private contribution
Punjab	266,100	223,219	157,512	65,707	84%	219	29.4%
Sindh	154,700	77,392	48,535	28,857	50%	175	37.3%
KP+ FATA	67,000	47,149	34,510	12,639	70%	143	26.8%
Balochistan	20,700	10,608	8,247	2,361	51%	93	22.3%
AJ&K	8,300	5,639	4,904	735	68%	151	13.0%
GB	2,500	2,685	2,400	285	107%	317	10.6%
ICT	5,700	2,205	1,799	406	39%	119	18.4%
TOTAL	525,000	368,897	257,907	110,990	68%	187	30.1%

Missing TB cases

There are more than 157,000 cases (1/3rd) of estimated TB cases that are either not notified or diagnosed in 2017. Based on estimates, there is a large number of missed cases in the age group 65 and above due to higher prevalence (1,100 / 100K) (4)

Figure-4: Notified and estimated missed TB Cases by Age and Sex -2017

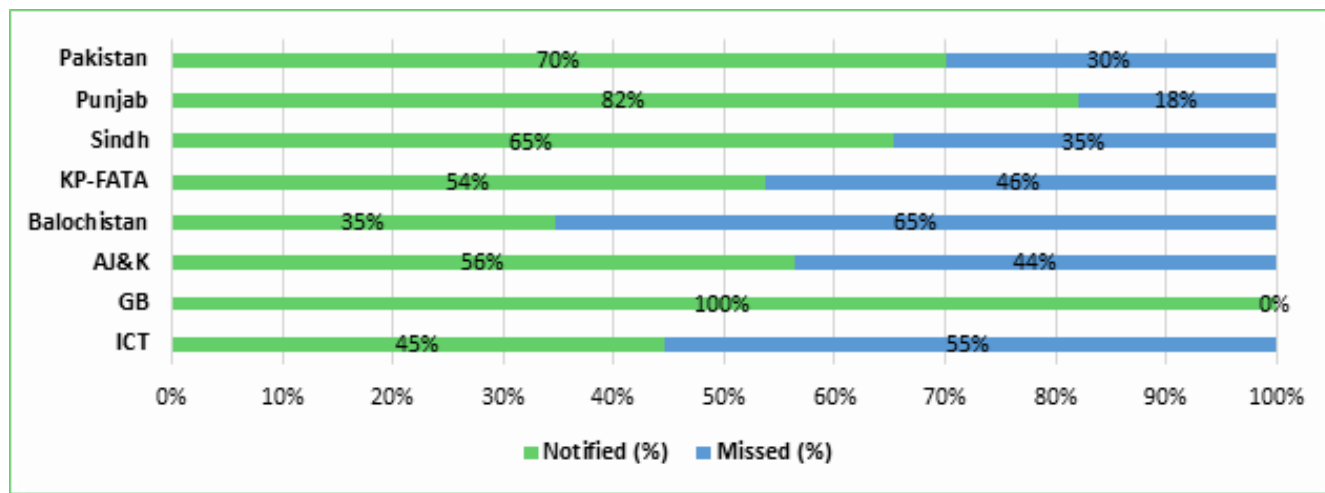


Missing TB cases by Province: TB cases notified by each province and region are shown in diagram below and percentage contribution to the national TB Missing cases.

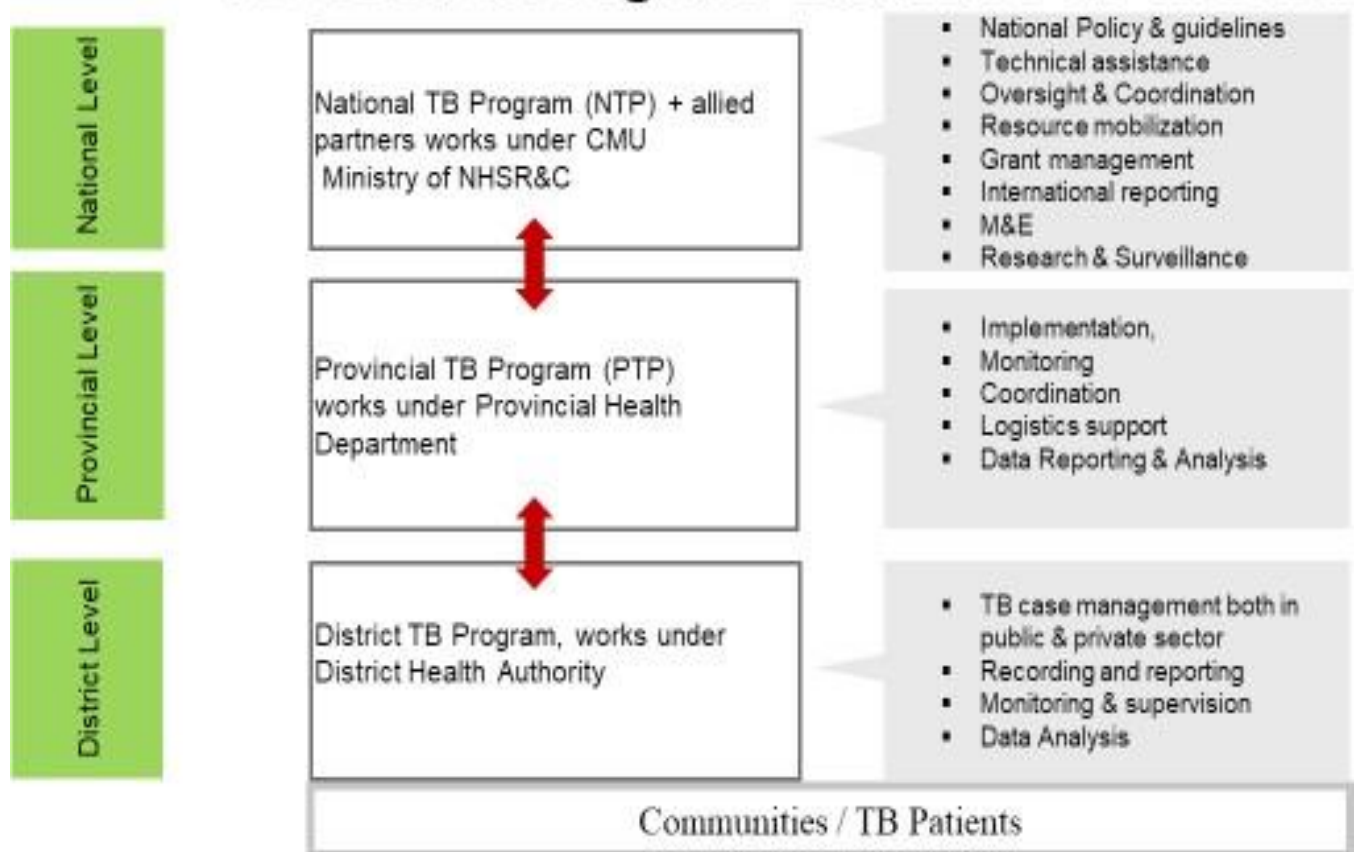
Figure 5: Missing TB cases by Provinces 2017

	Punjab	Sindh	KP (FATA)	Balochistan	AJ&K	GB*	ICT	Pakistan
Notified Cases	223,219	77,392	47,149	10,608	5,639	2,685	2,205	368,897
Missed Cases	48,792	41,018	40,698	19,902	4,356	-423	2,740	157,083
Missed (%)	18%	35%	46%	65%	44%	-19%	55%	30%

**Case detection is higher than estimated cases in GB*



TB Control Program- Structure & Function



2.1 SDGs and GLOBAL END TB STRATEGY

The 2030 Agenda for Sustainable Development (7), adopted by all United Nations Member States in 2015, provides a shared blueprint for peace and prosperity for people and the planet, now and into the future. At its heart are the 17 Sustainable Development Goals (SDGs), which are an urgent call for action by all countries - developed and developing - in a global partnership. They recognize that ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth – all while tackling climate change and working to preserve our oceans and forests. {SUSTAINABLE DEVELOPMENT GOAL 3 - Ensure healthy lives and promote well-being for all at all ages}.



The consolidated goal for health is SDG 3. There are 13 targets set under the goal while target 3.3 specifically mentions TB. “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases”.

The End TB strategy aims to end the global TB epidemic, provides a unified response to ending TB deaths, disease, and suffering with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB (8). It sets interim milestones for 2020, 2025, and 2030.

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%	50%	20%	50%
	(<85/100,000)	(<55/100,000)	(<85/100,000)	(<55/100,000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

The Strategy is built on three strategic pillars underpinned by four key principles.

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 & components

1. Integrated, patient-centered 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 co-morbidities
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

Globally, 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017 [global TB report 2018]. There were cases in all countries and age groups, but overall 90% were adults (aged ≥15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%).

Diagnosis and successful treatment of people with TB averts millions of deaths each year, but there are still large and persistent gaps in detection and treatment. Worldwide in 2017, 6.4 million new cases of TB were officially notified. Increase in notification is seen since 2013, mainly due to increased reporting of detected cases by the private sector in India and, in 2017, an upturn in notifications in Indonesia. The 6.4 million cases reported represented 64% of the estimated 10.0 million new cases that occurred in 2017. Ten countries accounted for 80% of the 3.6 million global gap, the top three being India (26%), Indonesia (11%) and Nigeria (9%).

Gaps between the estimated number of new cases and the number actually reported 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 when they do). Underestimation or overestimation of the total number of new cases is also possible.

Table-6: Top Ten priority indicators (9)

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%

2.2 WHO guidelines and standards of TB care (10)

Ensuring optimum delivery of the cascade of care for patients with tuberculosis. This Compendium is organized to follow the pathway of persons with signs or symptoms of TB in seeking care and to include crosscutting elements essential to the patient- centered approach to care delivery that is recommended by WHO (9).

WHO TB STANDARDS
Early detection of TB
WHO TB Standard 1 For persons with signs or symptoms consistent with TB, performing prompt clinical evaluation is essential to ensure early and rapid diagnosis.
WHO TB Standard 2 All persons who have been in close contact with patients who have pulmonary TB should be evaluated. The highest priority contacts for evaluation are those: <ul style="list-style-type: none"> • with signs or symptoms suggestive of TB; • aged < 5 years; • with known or suspected immune- compromising conditions, particularly HIV infection; • who have been in contact with patients with MDR-TB or extensively drug-resistant (XDR) TB.
WHO TB Standard 3 All persons living with HIV and workers who are exposed to silica should always be screened for active TB in all settings. Other high risk groups should be prioritized for screening based on the local TB epidemiology, health system capacity, resource availability and feasibility of reaching the risk groups.
WHO TB Standard 4 Chest radiography, or CXR, is an important tool for triaging and screening for pulmonary TB, and it is also useful to aid diagnosis when pulmonary TB cannot be confirmed bacteriologically. CXR can be used to select individuals for referral for bacteriological confirmation, and the role of radiology remains important when bacteriological tests cannot provide a clear answer.
Diagnosing TB disease
WHO TB Standard 5 To safely and efficiently diagnose TB and drug-resistant TB requires a functional network of quality assured laboratories with appropriate biosafety measures in place for performing different technical procedures. As such, TB Programmes require a tiered network of integrated laboratories in which different levels use complementary tools to diagnose TB and HIV, and have mechanisms for refer- ring specimens between the different levels of the network.

WHO TB Standard 6 All patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have as their initial diagnostic test at least one sputum specimen submitted for Xpert MTB/RIF Ultra assay. This also includes children who are able to provide a sputum sample. A second Xpert MTB/RIF Ultra assay may be performed for all patients who initially test negative by Xpert MTB/ RIF Ultra but whose signs and symptoms of TB persist.

WHO TB Standard 7 The Xpert MTB/RIF Ultra assay should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients being evaluated for TB meningitis. The Xpert MTB/RIF Ultra assay is recommended as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having EPTB.

WHO TB Standard 8 For persons living with HIV, the Xpert MTB/RIF Ultra assay should be used as an initial diagnostic test. The lateral flow urine lipoarabnomannan assay (LF-LAM) can be used to assist in the diagnostic process for HIV-positive patients who are seriously ill.

WHO TB Standard 9 DST using WHO- recommended rapid tests should be performed for all TB patients prior to starting therapy, including new patients and patients who require previously treated. If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid, fluoroquinolones and second- line injectable agents should be performed promptly to inform the treatment of MDR- TB and XDR-TB

WHO TB Standard 10 Culture-based (phenotypic) drug susceptibility testing for selected medicines should be performed for patients enrolled in treatment for drug- resistant TB.

Diagnosing latent TB infection

WHO TB Standard 11 Either a tuberculin skin test (TST) or an interferon gamma release assay (IGRA) can be used to test for latent TB infection (LTBI). A TST or IGRA is not a requirement before initiating tuberculosis preventive therapy in persons living with HIV and for children less than five years who are contacts of people with active TB disease

Treating TB - Treating drug-susceptible TB

WHO TB Standard 12 While awaiting DST results, patients with drug-susceptible TB and TB patients who have not been treated previously with anti-TB agents and do not have other risk factors for drug resistance should receive a WHO- recommended first-line treatment regimen using quality assured anti-TB agents. The initial phase should consist of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of 4 months of isoniazid and rifampicin. Daily dosing should be used throughout treatment. The doses of anti-TB agents should conform to WHO's recommendations. Fixed-dose combination (FDC) anti-TB agents may provide a more convenient form of administration.

WHO TB Standard 13 In patients who require previously treated for TB, the category II regimen should no longer be prescribed and DST should be conducted to inform the choice of treatment regimen

WHO TB Standard 14 In patients with tuberculous meningitis or tuberculous pericarditis, adjuvant corticosteroid therapy should be used in addition to an appropriate TB treatment regimen

Treating TB - Treating drug-resistant TB

WHO TB Standard 15 In patients with rifampicin-susceptible, isoniazid-resistant TB, 6 months of combination treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin, with or without isoniazid, is recommended.

WHO TB Standard 16 Patients with multidrug- or rifampicin-resistant TB (MDR/ RR-TB) require second-line treatment regimens. MDR/RR-TB patients may be treated using a 9–11 month MDR- TB treatment regimen (the shorter regimen) unless they have resistance to second-line anti-TB agents or meet other exclusion criteria. In these cases, a longer (individualized) regimen with at least five effective anti-TB agents in the initial phase and four agents in the continuation phase is recommended for 20 months or more. Partial resection surgery has a role in treating MDR-TB.

WHO TB Standard 17 A system to actively monitor and manage harms caused by anti-TB agents is required whenever drug- resistant TB patients are treated with novel or repurposed medicines and MDR-TB regimens.

Treating TB - Treating latent TB infection

WHO TB Standard 18 Persons living with HIV, HIV-negative children and adult household or close contacts of persons with pulmonary TB, as well as house- hold contacts of patients with multi-drug resistant TB and who, after an appropriate clinical evaluation, are found not to have active TB but to have LTBI should be treated.

HIV infection and other co-morbid conditions

WHO TB Standard 19 HIV testing should be routinely offered to all patients with presumptive TB and those who have been diagnosed with TB.

WHO TB Standard 20 Persons living with HIV should be screened for TB by using a clinical algorithm.
WHO TB Standard 21 Antiretroviral therapy (ART) and routine co-trimoxazole preventive therapy (CPT) should be initiated among all TB patients living with HIV, regardless of their CD4 cell count.
WHO TB Standard 22 A thorough assessment should be conducted to evaluate co-morbid conditions and other factors that could affect the response to or outcome of TB treatment. Particular attention should be given to diseases or conditions known to affect treatment outcomes, such as diabetes mellitus, drug and alcohol abuse, under nutrition and tobacco smoking.
Managing TB in children
WHO TB Standard 23 The diagnosis of TB in children relies on the thorough assessment of all evidence derived from a careful history (including history of TB contacts and symptoms consistent with TB), clinical examination (including growth assessment), a TST, CXR (if available), bacteriological confirmation whenever possible, investigations for suspected pulmonary TB and suspected EPTB, and HIV testing. Whenever possible, the Xpert MTB/RIF Ultra assay should be used as the initial diagnostic test in children suspected of having any form of TB.
WHO TB Standard 24 The principles of treating TB in children are the same as for treating TB in adults: first-line treatment of drug-sensitive TB consists of a 2-month initial phase with isoniazid, rifampicin, pyrazinamide and, depending on the setting and type of disease, ethambutol, followed by a continuation phase with isoniazid and rifampicin for at least 4 months; however, the dose of first-line anti-TB agents differs from that administered in adults.
WHO TB Standard 25 In settings where TB is highly endemic or where there is a high risk of exposure to TB, a single dose of bacille Calmette–Guérin (BCG) vaccine should be given to all infants; however, HIV-positive children should not be given BCG vaccine. After considering local factors, BCG vaccine should be given to all infants except those who are HIV-positive for whom BCG is contraindicated
WHO TB Standard 26 All children younger than 5 years and HIV-positive children of any age should be included in contact screening and management efforts, with the aim of identifying undiagnosed TB disease and providing preventive therapy for contacts without TB disease who are susceptible to developing disease following exposure to a contact with active TB disease.
Monitoring and evaluation
WHO TB Standard 27 All providers must report both new and re-treatment TB cases and their treatment outcomes to national public health authorities in conformance with applicable legal requirements and policies; TB mortality should be monitored by using standard cause-of-death data from vital registration systems.
Supportive approaches – Digital health
WHO TB Standard 28 Digital technologies can be adapted to increase the effectiveness or efficiency of different components of TB Programmes
Supportive approaches – Infection control
WHO TB Standard 29 Promptly identify persons with TB symptoms (triage); provide an adequately ventilated waiting area for them; educate them about cough etiquette and respiratory hygiene; ensure they are prioritized for TB testing; and separate infectious patients
Supportive approaches – Patient care and support
WHO TB Standard 30 A patient-centered approach to treatment should be developed to promote adherence, improve quality of life and relieve suffering. This approach should be based on the patient’s needs and on mutual respect between the patient and the provider
WHO TB Standard 31 Prior to starting TB treatment, each patient’s need for support should be assessed, and interventions to encourage adherence to treatment be offered to improve outcomes
WHO TB Standard 32 Before starting TB treatment, all patients should be assessed to determine the risk of treatment interruption, and appropriate options for treatment administration should be offered to each patient. Community- or home-based DOT is recommended over health facility- based DOT or unsupervised treatment; and DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members. Video-observed treatment may replace DOT when the technology is available and can be organized and operated by health- care providers and patients
Supportive approaches – Palliative care
WHO TB Standard 33 All forms of suffering associated with TB should be addressed by ensuring that patients have proper access to care and to the management of adverse reactions to treatment, management of psychological distress, means to prevent and mitigate stigma and discrimination, and by providing access to social protection mechanisms to reduce indirect costs (10)

2.3 NTP Pakistan's Response– National END TB Strategic Plan (2017-2020)

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. At the federal level, a SDGs Monitoring and Coordination Unit, in coordination with UNDP, is being set up to serve as a national coordinating entity with similar units in the provinces.

Ministry of National Health Services Regulations & Coordination is committed to implementing SDG3 agenda through its localization and integration with the country health strategies and plans at National and Provincial level.

The aim of the First WHO **Global Ministerial Conference** (11) on Ending TB in the Sustainable Development Era: A Multisectoral Response was to accelerate the response to meet the targets agreed under the End TB Strategy and Sustainable Development Goals, through increased national and global commitments (12).

Pakistan is signatory to the Moscow declaration to End TB. Pakistan joined the member states to endorse the Political Declaration on the Fight against Tuberculosis (TB) at the UN first High-Level Meeting for TB held on 26th September; 2018 (13) we have conducted extensive follow up with concerned delegations. After several attempts and with much effort from these delegations, we have arrived at what we believe is an acceptable accommodation of the interests of all parties. We therefore have the honour to transmit the attached text which is based on the consensus achieved, and to request that it be placed under silence until 10 a.m. on 14 September 2018. We wish to take this opportunity to express sincere thanks to all delegations for their spirit of flexibility and their commitment to a positive outcome.

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National TB strategic plan to End TB (2017-2020) is aligned with WHO End TB strategy and plan proposes bold strategies to end TB in the country in line with SDGs and End TB strategy (14).

Vision: TB free Pakistan- zero TB deaths, disease and poverty caused by TB

Goal: To end the TB epidemic by 2035.

Target: To reduce the TB incidence by 20% in 2020 (from the baseline of 270/100,000 in 2015).

Chapter-3 Basics about TB disease

Causative organism and mode of spread

Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis*. TB bacteria are spread through the air from one person to another. Tuberculosis is a highly contagious infection, transmitted to other healthy persons by infected droplets generated by coughing or sneezing of patient having active pulmonary Tuberculosis disease. These tiny droplets dry rapidly, attach themselves to fine dust particles and the smallest of them may remain suspended in the air for several hours. Only those particles that are less than 10 µm (micron) in diameter reach the pulmonary alveoli of the healthy individual through inhalation resulting in infection. While not everyone exposed to the bacterium becomes infected nor does everybody infected with it develop clinical symptoms. The chance of becoming infected depends mainly on the quantity of infectious droplets in the air, and the length of exposure to an infectious person. The closer the infectious person is, and the longer the length of exposure, the higher the risk is of being infected.

When a person breathes in TB bacteria, the bacteria can settle in the lungs and begin to grow. Tuberculosis spreads from the primary lung lesion to other parts of the body via the blood stream, lymphatic or by direct extension, and in this way may affect any organ in the body. TB is thus classified as pulmonary (Lungs parenchyma) and extra-pulmonary on the basis of anatomical site involved.

TB disease in the lungs or throat can be infectious. This means that the bacteria can be spread to other people. TB in other parts of the body, such as the kidney or spine, is usually not infectious. People with TB disease are most likely to spread it to people they spend time with every day. This includes family members, friends, and co-workers or schoolmates. TB is NOT spread by shaking someone's hand, sharing food or drink, touching bed linens or toilet seats, sharing toothbrushes or kissing.

3.1 Latent TB Infection and TB disease

LTBI is a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of active TB. The majority of infected people have no signs and symptoms of TB but are at risk of developing active TB and may become infectious. On average, 5 to 10% of those who are TB-infected will have active TB over the course of their lives, usually within the first five years after infection. The risk of occurrence of active TB depends on several factors, the most important being the immunological status of individuals.

TB Disease: TB bacteria become active if the immune system cannot stop them from growing. When TB bacteria are actively multiplying in the body, this is called TB disease. People with TB disease are sick. They may also be able to spread the bacteria to people they spend time with every day.

Many people who have latent TB infection never develop TB disease. Some people develop TB disease soon after becoming infected (within weeks) before their immune system can fight the TB bacteria. Other people may get sick years later when their immune system becomes weak for another reason.

For people whose immune systems are weak, especially those with HIV infection, the risk of developing TB disease is much higher than for people with normal immune systems.

3.2 Signs and Symptoms

The symptoms of TB vary depending on which part of the body is affected. TB disease usually develops slowly; symptoms might not begin until months or even years after the initial infection.

Pulmonary Tuberculosis

TB bacteria usually grow in the lungs (pulmonary TB). TB disease in the lungs may cause symptoms such as:

- cough more than two or more weeks, or of any duration with following symptoms
- pain in the chest
- coughing up blood or sputum (phlegm from deep inside the lungs)

Other symptoms of TB disease are:

- weakness or fatigue
- weight loss
- reduced appetite
- chills
- fever
- sweating at night

Extra Pulmonary Tuberculosis

Symptoms of TB disease in other parts of the body depend on the area affected. Following are the main forms of extra-pulmonary TB are listed below with symptoms:

	EPTB Disease SITE	Specific symptoms
1	Lymph nodes-Extra-thoracic	Swelling, matted occasionally with pus drainage
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 include 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 effected side)
8	Other	Infertility in case of reproductive tract. Symptoms of urinary tract infection in case of genito-urinary involvement
9	Miliary /Multiple	Miliary tuberculosis (TB) is the widespread dissemination of Mycobacterium tuberculosis via haematogenous spread, seeding of TB bacilli in the lung, as evidenced on chest radiography.

Asymptomatic TB Cases

The TB patients may present with atypical symptoms, which makes diagnosis difficult. It has also been reported in disease prevalence survey in which all patients undergo both symptom and X-ray screening that significant number of bacteriological confirmed TB cases had not complaint of any symptoms and were investigated based on abnormalities on X-ray. In view of the evidences from prevalence surveys (4), mass X-Ray screening is now being used in high risk target population for identification of presumptive TB cases among asymptomatic (4,15). It is important to mention that indiscriminate X-Ray screening is not recommended.

3.3 TB Risk factors

Some people develop TB disease soon after becoming infected (within weeks) before their immune system can fight the TB bacteria. Other people may get sick years later, when their immune system becomes weak for another reason.

For persons whose immune systems are weak, especially those with HIV infection, the risk of developing TB disease is much higher than for persons with normal immune systems. Generally, persons at high risk for developing TB disease fall into two categories:

(1) Persons who have been recently infected with TB bacteria includes:

- Close contacts of a person with infectious TB disease

- Children less than 5 years of age who have a positive tuberculin test
- Groups with high rates of TB transmission, such as homeless persons, injection drug users, and persons with HIV infection
- Persons who work or reside with people who are at high risk for TB in facilities or institutions such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV

(2) Persons with medical conditions that weaken the Immune System: Babies and young children often have weak immune systems. Other people can have weak immune systems, too, especially people with any of these conditions:

- HIV infection (the virus that causes AIDS)
- Substance abuse
- Silicosis
- Diabetes mellitus
- Severe kidney disease
- Low body weight
- Organ transplants
- Head and neck cancer
- Medical treatments such as corticosteroids or organ transplant
- Specialized treatment for rheumatoid arthritis or Crohn's disease

3.4 TB case definitions

Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB and/ or abnormal chest x-rays suggestive of TB.

Note: *The asymptomatic people with high risk of developing TB on the basis of their living conditions & other comorbidities should be included & tested for TB Case definitions*

Bacteriologically confirmed TB case (B+) is one from whom a biological specimen (sputum, pleural fluid, peritoneal fluid, pus, cerebrospinal fluid etc.) is positive at smear microscopy, culture or WHO approved rapid diagnostic (WRD) such as X-pert MTB/RIF.

Note: *All such cases should be notified, regardless of whether TB treatment has started.*

Clinically diagnosed TB case is one who does not have bacteriological confirmation but has been diagnosed with active TB by a clinician. This definition includes TB cases diagnosed on the basis of radiological (X-ray, CT-Scan, MRI. Ultra-sound scan) abnormalities or suggestive histology without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified and notified as bacteriologically confirmed TB case.

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

Extra-pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs.

New TB case: The patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Previously treated TB case: TB patients who have received 1 month or more of anti-TB drugs in the past. Previously treated cases are further classified by the outcome of their most recent course of treatment as follows:

- **Relapse** -TB patients who were previously treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment. Relapse may either be due to reinfection or reactivation of dormant bacilli.
- **Treatment after failure**- TB patients who were previously treated for TB and treatment failed at the end of their most recent course of treatment.
- **Treatment after loss to follow-up** - TB patients who were previously treated for TB and but interrupted treatment and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)
- **Other previously treated** - TB patients who were previously treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
Patients with unknown previous TB treatment history do not fit into any of the categories listed above (these patients will be treated as New cases).

Incident TB cases: New, Relapse & patients with Unknown previously treatment history are counted as incident TB cases.

Index case (index patient): The initially identified case of new or previously treated TB of any age in a specific household or other comparable setting in which others may have been exposed

Contact: Any person who has been exposed to an index case (as defined above)

Household contact: A person who shares the same living space for one or more nights or for frequent or extended periods during the day with the index case during the past 3 months before commencement of the current treatment episode (once effective treatment is started; index case is less likely to transmit infection to contacts)

Close contact: A person who is not in the household but shared a space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the past 3 months before commencement of the current treatment episode.

TB Care and Prevention

Chapter-4 TB case finding approaches

In Pakistan, based on population estimates of 197 Million and TB incidence rate of 267/100K population, 525,000 new TB cases were developed in 2017 and 369,897 (68%) TB cases were notified. This accounts for more than 157,000 TB cases missed to notification during year 2017 in Pakistan.

In 2017, 6th population and housing census was conducted in Pakistan, and based on the census results estimated country's population was revised upwards to 207 M. Increase in Population estimates means increase in estimated TB disease burden and further widening of gap between estimated and notified cases. Concerted efforts are needed to improve TB case finding and diagnosis to meet milestone of treatment coverage of 90% by 2025.

Top priority actions include;

1. Notification of all TB cases treated including those treated outside national surveillance systems through mandatory notification of TB cases.
2. Enhance case finding efforts for diagnosis of TB cases accessing health care in public or private sector but are missed in health system.
3. Active case finding for TB cases in the community.

To achieve the 1st milestone of END TB Strategy by 2020 (reduction in number of TB deaths by 35% compared to 2015, reduction in TB incidence by 20% compared to 2015 & Zero % of TB patients and their households experiencing catastrophic costs due to TB), optimum use of existing interventions, achievement of universal Health coverage (UHC) for essential prevention, treatment and care interventions as well as efforts to address social determinants and consequences of TB will be required. A wider multi-sectoral collaboration is essential through including ministries, civil society, communities and the private sector to reach milestones set in the END TB strategies (12).

To improve tuberculosis control, patient with active TB disease must be diagnosed quickly and treated immediately. TB case finding effort were mostly limited to passive case finding approaches and stagnant TB case notification is seen in the public sector for past several years. It is evident there are undiagnosed cases in the community and there is need to reach community to find missed TB cases in marginalized/high risk population (16). Main difference between passive and active case finding approaches are described below.

Passive Tuberculosis case finding

Relies on sick people seeking health care, examination is recommended for:

- Presumptive TB cases (cough > two weeks or any duration with relevant symptoms) who present themselves at health facilities
- Patient with abnormal shadows on chest X-Ray consistent with Tuberculosis.

Passive approaches, for TB case finding depends on patients to seek care and depends on awareness about TB symptoms, health seeking behavior, access to the TB care facilities, in addition the passive case finding also depends at the knowledge and practices of the health care providers, it is known that many patients with symptoms of TB presenting at health facilities are missed to identification as presumptive and thus not evaluated for TB. Some patients who present with atypical symptoms are also missed to diagnosis of TB. It is important to understand that unidentified TB patient poses greater risk of transmission of disease, higher the duration higher the risk.

Active Tuberculosis case finding

Active case finding is predominantly provider initiated with goal to reduce TB diagnostic delay and reduce TB transmission in the community. Active TB case finding aims to reduce barriers to access TB care due either to lack of awareness or difficulties to access health care.

The Program recommends active case findings among pre-determined target groups

- Household contacts of all bacteriologically confirmed pulmonary TB patients. (In case of CHTB case reverse contact screening to find source TB case)
- Marginalized population e.g. Urban slums
- High vulnerable population prisons and institutes
- Internally displaced population

Different interventions are used for TB case finding in the community e.g. Community workers/ volunteers/LHWs/ are mobilized for TB contact tracing and special chest camps are organized to find TB cases in urban slums, workplaces, hot spots identified by Epi data, and congregate settings. Indiscriminate active case finding in general population is not recommended

5.1 AFB smear microscopy

AFB smear Microscopy is globally recognized as a transmission-risk indicator, as it quickly detects infectious cases of pulmonary TB, which contain sufficiently large numbers of acid-fast bacilli to be readily detected by microscopy e.g. sputum specimens from PTB patients having cavitary disease.

Principle and methods

The mycobacterial cell wall contains mycolic acids, which are fatty acids that contribute to the characteristic of “acid-fastness.” The principle of the AFB smear is based on the fact that mycolic acid in the cell wall of AFB render them resistant to de-colorization with acid alcohol. Staining procedures used for the screening and/or confirmation of AFB are:

- **Ziehl-Neelson (Conventional light microscopy):** Classic procedure that allows stain to persist after heating (required for better penetration of the stain into the cell wall. Convention bright field microscopes are used to examine ZN stained smears.
- **Fluorochrome (Light-emitting diode (LED) fluorescent microscopy):** This screening procedure that is more sensitive (10%) than conventional carbol fuchsin stains (Ziehl-Neelsen or Kinyoun fluorescence microscopy is on average 10% more sensitive than ZN microscope.

AFB microscopy services

Microscopy services are well established in the country with an average of one microscopy laboratory for 120K population. All health facilities were initially equipped with bright field microscopes for examination of ZN stained smears. After the endorsement of WHO, Programme has successfully introduced LED fluorescent microscopes in more than 50% of the microscopy centers.

Limitation of AFB microscopy

Direct smear microscopy is relatively insensitive and more than 5,000 bacilli per milliliter of sputum are required to detect AFB. Smear microscopy is thus less sensitive to diagnose paucibacillary form of TB diseases e.g. in children, patients with HIV-co-infection and extra-pulmonary TB. Furthermore, AFB microscopy cannot distinguish Mycobacterium tuberculosis from NTM, viable from non-viable organisms, or drug-susceptible from drug-resistant strains.

Recommendation on Use of AFB microscopy

Keeping in view the advantages (low cost, better coverage, early detection of infectious cases) and disadvantages (low sensitivity) of AFB microscopy, cost implication and availability of Xpert testing facilities, challenges in specimen transport systems and turnaround time, AFB microscopy is recommended as:

- Front line tool for diagnosis of all type patients presumed to have TB, seeking health care from facilities where Xpert MTB/RIF testing is not available on site. However, after making smear for microscopy same specimen may be referred for Xpert testing as per national guideline (see below)
- Front line test for diagnosis of PTB in Adult patients presumed to have TB not at risk of Drug resistant TB and not immunocompromised
- Test for monitoring treatment response of;
 - PTB patients on first line drugs
 - Drug resistant PTB patients on second line drugs along with culture.

5.2 X-PERT MTB/RIF ASSAY

The X-pert MTB/RIF is the only WHO-recommended Rapid Molecular Diagnostic Test that simultaneously detects TB and resistance to rifampicin in less than two hours. GeneXpert is currently the only fully automated cartridge based real-time DNA based test. It is more sensitive than microscopy and with detection limit of 136 (MTB/ML of sputum) and thus has a high sensitivity in smear-negative tuberculosis. The sensitivity of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, United

States) for detecting TB is similar to that of solid culture (88% when compared with liquid culture as a reference standard). The specificity is also high (99%) Sensitivity of a single X-pert MTB/RIF test in smear-negative/ culture-positive patients is reported to be 72.5% and increased to 90.2% when three samples are tested.

The Xpert MTB/RIF Ultra assay has a higher sensitivity than the Xpert MTB/RIF assay, particularly in smear-negative, culture-positive specimens and in specimens from HIV-positive patients. It has at least as good accuracy for detecting rifampicin resistance. However, as a result of the increased sensitivity, the Xpert MTB/ RIF Ultra assay also detects non-replicating and non-viable bacilli, particularly in patients with a recent history of TB, which reduces the overall specificity of the Xpert MTB/RIF Ultra assay in high-burden settings. Nonetheless, in low burden settings and when testing specimens to diagnose EPTB and pediatric TB, false positive results were not a major concern.

Recommendation on use of X-pert MTB/RIF

WHO endorsed the use of X-pert MTB/RIF assay in 2010. WHO Policy recommendations on the X-pert MTB/RIF assay (X-pert MTB/RIF) were issued in early 2011 and were updated in 2013.

WHO recommends use of X-pert MTB/RIF as an initial diagnostic test in individuals (adults and children) presumed to have TB or DR-TB or HIV-associated TB. However, subject to resource implication use of X-pert MTB/RIF is recommended as a follow-on test to microscopy in adults presumed to have TB but not at risk of DR-TB or HIV associated TB.

Based on WHO recommendation and keeping in view coverage and resource implication following is recommended:

Use of Xpert as initial diagnostic test

- Individual presumed to have Drug resistant PTB (Adults and children) including those with previous history of TB treatment, Contact of RR/MDR TB patient, Health care workers
- Children (less than 15 years) presumed to have TB
- Immunocompromised individual presumed to have TB
- Individual (adults and children) presumed to have Extra pulmonary TB cases
- Individual Presumed to have PTB with CXR showing changes suggestive of TB

Use of Xpert as follow on to microscopy

- AFB smear positive TB cases
- AFB smear Negative cases with CXR showing changes suggestive of TB

Table-7: Reporting and interpretation of X-pert MTB Rif results

DR-TB risk assessment	Interpretation	Treatment decision
Report-1: MTB Detected - Rif resistance NOT detected		
No previous history of ATT	Definite TB case NO Rifampicin resistance	Start treatment of new case
Past History of TB episode including (TAF, TAD, Others)	Definite TB case NO Rifampicin resistance	Start treatment as previously treated case Fresh sample for comprehensive DST, adjust treatment based on DST results.
Report-2: MTB Detected - Rifampicin Resistance Detected		

No previous history of ATT	Definite TB case with Rifampicin resistance	*Repeat X-pert MTB/Rif assay on fresh sample in same laboratory– If -RR Not detected - start on FLD- treatment of new case -RR detected – Register patient in TB 03 TB-register, then –“Transfer out” to PMDT site for DRTB treatment.
History of previous ATT	Definite TB case with Rifampicin resistance	Register patient in TB 03 TB-register, then –“Transfer out” to PMDT site for DRTB treatment
MTB Detected - Rifampicin Resistance (indeterminate)		
	Definite TB case but Rifampicin status not reported	Register patient on TB treatment, based on history of previous treatment history (as above) Repeat Xpert on fresh sample –if same results- and patient is at risk of MDR send sample for phenotypic DST.
MTB Detected –TRACE (Rifampicin Resistance (indeterminate))		
No Past history of TB	Definite TB case	Repeat on Fresh morning sample – If same results Register as treatment of new case
Past history of TB Treatment		Repeat on Fresh morning sample – If same results exclude possibility of dead bacilli in case of recent history of TB by careful history and clinical evaluation. Register as treatment for new case- send sample for phenotypic DST.
Report-3: MTB not detected		
Irrespective of previous history of TB treatment	MTB not detected, TB not excluded but unlikely	Consider repeat Xpert testing if TB is highly suspected OR call for follow up after 2 weeks if symptoms persist and repeat clinical assessment.
Report-4: MTB not detected in AFB smear positive specimen		
Irrespective of Previous history of TB treatment	Possibility of Mycobacteria other than TB	Repeat AFB smear microscopy and Xpert/MTB Rif-assay – If same result- refer patient for management of MOTT

*Rifampicin resistance detected in patients not at risk of drug resistance should be repeated on fresh sample in same laboratory/ Xpert sites. This practice will help to exclude any possibility of administrative error in identification of sample or reporting before referring patients for treatment of RR-TB. Confirmation of RR report before referral will help avoid unnecessary inconvenience to patients of going to DRTB treatment site and delay in first line TB treatment in case of any error.

5.3 Culture and Species Identification

Mycobacterial culture and identification of *M. tuberculosis* provide a definitive diagnosis of TB and is currently considered reference gold standard for diagnosis. Solid (Lowenstein Jensen and Agar) and Liquid media are used for culture. Detection limit of Liquid Culture is 10 bacilli/ml. Liquid culture increases the case yield by 10% over solid media, and automated systems reduce the diagnostic delay to days rather than weeks. Liquid systems are, however, more prone to contamination and the manipulation of large volumes of infectious material mandates appropriate and adequate biosafety measures. The main limitation of culture as diagnostic tool in routine practice is slow growth of bacilli with long reporting time (1-2 weeks on liquid and 4-8 weeks on solid culture media). Furthermore, culture services demand technically complex infrastructure, expertise and resources, therefore use of culture as initial diagnostic test for diagnosis in routine programme condition is not recommended not feasible therefore not recommended.

However, culture services are essential for programmatic management of drug resistant TB as culture provides the necessary isolates for identification and drug susceptibility testing and is also used for monitoring treatment response of drug resistant TB patient.

Coverage of culture services

National TB Control Programme has established 22 culture laboratories across country and 7 of these laboratories have DST capacity. The DST laboratories are located in national/ provincial reference laboratories and have both liquid and solid culture facilities, whereas other 15 laboratories are equipped with solid culture facilities only.

5.4 Other laboratory Test for diagnosis of Tuberculosis

Histopathology

Histological examination can play a role in diagnosis of tuberculosis (caseating granulomas) in the absence of bacteriology examination or negative result. However, histology is non-specific and patient's risk of tuberculosis should be considered to avoid misclassifying non-caseating granulomatous processes due to tuberculosis as sarcoidosis, Crohn's disease, or other granulomatous disease or other way round.

With availability of more sensitive molecular tools, probability of diagnosing pauci bacillary TB disease has improved, it is strongly recommended that in all presumptive TB patient with extra pulmonary disease, aspirated /biopsied specimen (collected in normal saline) should be referred for Xpert MTB/Rif assay for definite diagnosis of TB.

Test having no role in the diagnosis of Tuberculosis

- **Serological Test:** Dozens of commercial serological tests for tuberculosis are being marketed in many parts of the world. An updated systematic review was commissioned by WHO to synthesize the evidence on the diagnostic accuracy of commercial serological tests for pulmonary and extra-pulmonary tuberculosis. Commercial serological tests provide inconsistent and imprecise findings resulting in highly variable values for sensitivity and specificity. It is strongly recommended that these tests should not be used for the diagnosis of pulmonary and extra-pulmonary TB.
- **Other Lab tests:** Blood examination e.g. Hemoglobin, white blood counts and ESR are nonspecific tests. Anemia is more likely to be due to other causes than TB, WBC is usually normal or lower than normal in TB and ESR is usually raised in TB but high ESR is also seen in many other condition and normal result.

5.5 Tool for Diagnosis of Drug Resistant TB

Drug-susceptibility testing (DST) serves three main purposes: first, it can be used to guide the choice of chemotherapy for a patient. Second, it is valuable in confirming that resistance has emerged when a patient has failed to have a satisfactory response to treatment. Third, it can be used for the surveillance of resistance to anti-TB medicines. Two main methods for detection of anti-microbial drug resistance are Conventional culture based methods and new molecular based rapid method.

Culture-based (phenotypic) drug susceptibility testing

DST uses critical concentrations of anti-TB medicines to determine the susceptibility or resistance of a M. tuberculosis culture isolates. The critical concentration is defined as the lowest concentration of anti-TB medicines in vitro that will inhibit the growth of 99% of phenotypically wild type strains of M. tuberculosis complex.

Critical concentration is defined for first line drugs (FLD) including Rifampicin, Isoniazid, ethambutol, and Pyrazinamide and second line drugs (SLD) including Ofloxacin, Levofloxacin, Moxifloxacin, Amikacin, Clofazamine, linezolid, Bedaquiline and Delamanid

Molecular (genotypic) drug susceptibility testing

- **Xpert MTB/RIF assay:** As mentioned above Xpert simultaneously detect MTB and Rifampicin resistance in MTB positive specimen. Rifampicin is a good proxy indicator for MDR, and second line treatment is recommended for both RR and MDR patients. All bacteriologically confirmed TB cases should be tested at time of registration for Rifampicin resistance. For patient tested upfront with Xpert, Rifampicin results will be available but those diagnosed on microscopy should be screen for Rifampicin resistance using Xpert MTB/Rif assay.
- **Line Probe Assay:** Commercially available molecular Line Probe Assay (LPAs) have good accuracy when used for either from Clinical specimen (direct) or culture isolates of M. tuberculosis complex (indirect testing) for resistance to anti TB agents. WHO recommends using commercially available molecular line probe assays (LPAs) as the initial

test, instead of phenotypic culture-based DST to detect resistance to First (rifampicin and isoniazid) and second line anti-TB agents (fluoroquinolones and second-line injectable agents). Second-line LPA can be used to identify persons eligible for enrolment on the shorter MDR-TB regimen.

5.6 Laboratory test for diagnosis of TB infection

No tool allows direct measurement of *M. tuberculosis* infection in humans, and the diagnosis of LTBI is based on a positive result by either tuberculin skin test (TST) or interferon gamma release assay (IGRA), indicating an immune response to *M. tuberculosis*. However, these tests cannot accurately predict the risk of developing active TB disease.

Tuberculin Skin Test

TST is based on the detection of delayed-type hypersensitivity to PPD, a mixture of antigens shared by several mycobacteria that gives rise to a skin reaction. TST is not expensive, requires an injection into the skin and adequately trained staff. However, it requires two visits of patient one for injection and second after 48-72 hours for reading of results.

- **Interpretation of TST (Annex Montoux Chart):**

- ≥ 5 mm (MOTT)
- ≥ 10 mm (mycobacterial infection in non BCG vaccinated persons) &
- ≥ 15 (mycobacterial infection in BCG vaccinated) have been recommended

BCG vaccination may cause false-positive results in younger persons.

Tuberculosis Interferon Gamma Release Assays

(17) based on the principle that the T-cells of individuals who have acquired TB infection respond to re-stimulation with *Mycobacterium tuberculosis*-specific antigens by secreting interferon gamma (IFN- γ)

Research over the past decade has resulted in the development of two commercial interferon gamma release assays (IGRAs), based on the principle that the T-cells of individuals who have acquired TB infection respond to re-stimulation with *Mycobacterium tuberculosis*-specific antigens by secreting interferon gamma (IFN- γ).

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

- **Testing for TB in BCG-Vaccinated People:** Vaccination with BCG may cause a positive reaction to a TB skin test. A positive reaction to a TB skin test may be due to the BCG vaccine itself or 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. For children under the age of five, the TB skin test is preferred over TB blood tests.

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 latent TB infection or has progressed to TB disease. Other tests, such as a chest x-ray and a sample of sputum, are needed to see whether the person has TB disease.

Chapter-6 Role of X-Rays in Diagnosis of Tuberculosis

Chest radiography, or chest X-ray (CXR) (18), is an important tool for;

- i. For the clinical management of a person seeking healthcare for one or several unexplained complaints or concerns
- ii. For screening in the pre identified groups in community /special setting for active TB case finding.
- iii. For Clinical diagnosis of TB in bacteriologically negative TB cases as well as diagnosis non-TB chest diseases

CXR, is a good screening tool for pulmonary TB because of its high sensitivity (87% to 98%) (18) meaning that up to 98% of those with culture-positive TB have an abnormal CXR. However, CXR has low specificity in an active case-finding situation (46% to 89%, depending on how it is read), meaning that a significant proportion of individuals without TB will have an abnormal test result. This is due, in part, to the fact that CXR identifies many types of lung abnormalities, whether due to TB or to other lung conditions. However, CXR screening will filter out patients having high probability of suffering from TB and thus will reduce the cost on number tests required to detect a bacteriologically confirmed TB case.

All patient having abnormal CXR suggestive of TB should be investigated with a bacteriological confirmatory test that has high sensitivity and specificity for TB. Diagnosis of PTB based on CXR and clinical criteria alone in patient who screen positive by CXR but are negative by bacteriological tests need to be carefully evaluated and these should not constitute more than a very small fraction of all notified PTB cases. From the perspective of the person being screened, CXR is a valuable tool because it provides rapid screening results for a range of medical conditions and not a TB-specific tool. It can be used to improve care for patients with respiratory diseases.

Technology

Two types of technology are used for CXR: analogue (that is, a system using film) or digital. It is important to highlight that both of these technologies employ the same principle of X-ray production; the difference is the method of recording the result. In conventional systems, the result is recorded and displayed on an X-ray film but in digital systems, the result is recorded on a detector and displayed in a digital format on a computer screen (and it can also be printed on X-ray film or paper or sent to a digital device).

Digital systems have several advantages over conventional systems. They reduce procedure time, have very low running costs (particularly when a hard copy image is not needed), save on staff requirements because the system is more user-friendly, produce superior image quality, give a lower radiation dose, allow for easier archiving and are more environmentally friendly. Moreover, they allow for telemedicine solutions and can be used for computer-aided reading.

Computer-aided detection of TB (CAD4TB)

New technologies for analyzing the results of CXR evaluations are being developed, including computer aided detection (CAD) software that can analyze digital CXR images for abnormalities and the likelihood of TB being present. An abnormality score ranging from 0 to 100, with higher scores indicating greater likelihood of TB (>70). A threshold score is the score below which TB is ruled out. Such technology could help reduce inter reader variability and delays in reading radiographs when skilled personnel are not available.

Chapter-7 Diagnosis of Tuberculosis

7.1 Considerations for recommended TB Diagnostic approaches and algorithm

All patient presumed to have TB should be carefully assessed for:

- Risk of drug resistant tuberculosis (history of previous treatment, MDR contact)
- Immune status and vulnerability to severe form of tuberculosis (Children, HIV + and other immune-suppressed, seriously ill, hospitalized)
- Difficulties in diagnosis e.g. Extra-pulmonary Tuberculosis and even PTB in adults having difficulty in expectorating sputum or where sputum/bronchial specimen are obtained using special intervention (Gastric aspirate, BAL, Bronchial biopsy).

Presumptive TB cases	Risk of Drug resistance	Increased risk of TB (Im-mune-com-promised / contacts)	CXR-sug-gestive of TB	Xpert Testing Facility	Recommended Initial Diagnostic test	Further action
Pulmonary TB case						
ADULT	NO	NO	NOT Avail-able /NOT Done	On-site /Remote Linked Lab	AFB microscopy	If SSM+, Xpert MTB/RF for RR If SSM-ve, Clinical evaluation/CXR-Xpert MTB/RF for RR
ADULT	NO	NO	YES	On site	MTB/RIF assay	Repeat MTB/RIF if RR
				Remote linked laboratory (TAT >24hours)	AFB microscopy	Refer Same specimen for Xpert MTB/RIF assay
ADULT	NO	YES	+/-	On site	MTB/RIF assay	Repeat MTB/RIF if RR
				Remote linked laboratory (TAT >24hours)	AFB microscopy	Same specimen for Xpert MTB/RIF assay
ADULT	YES	+/-	+/-	On site	MTB/RIF assay	If RR+, Register in TB register/ transfer out to PMDT-DRTB register
				Remote linked laboratory (TAT >24hours)	AFB microscopy	Same specimen for Xpert MTB/RIF assay
Children <15 years	+/-	+/-	+/-	On site	MTB/RIF assay	Repeat MTB/RIF if RR
				Remote linked laboratory (TAT >24hours)	AFB microscopy If enough quantity specimen	Same specimen for Xpert MTB/RIF assay
Extra-Pulmonary TB case						
Adult /Chil-dren	+/-	+/-	+/-	On site	MTB/RIF assay	Culture
				Remote linked laboratory	All specimen refers to Xpert site. AFB microscopy only If in sufficient quantity purulent material	Same specimen for Xpert MTB/RIF assay

Consideration for Diagnosis of Pulmonary TB (PTB)

All adult patients presumed to have pulmonary TB /with chest radiographic findings suggestive of TB (Figure-6) should have sputum specimens examined in a quality-assured laboratory (ISTC standard-2).

a) For AFB microscopy

Two sputum specimen should be examined as follows:

- **Spot Specimen:** Sputum sample is collected on first day a
- **Early morning Specimen:** Sputum sample is collected early morning next day at home. Morning specimen has the highest yield and should be tested whenever feasible.

“Same Day Diagnosis” or front loading technique is an approach when two sputum specimens are collected (with one-hour gap) and examined on the same day (also known as front loading technique). It may be applied in situation where specimen collection on over two days is not convenient either because patient has travelled long distance to reach health facility or in chest camps or other special situation (active case finding).

b) For Xpert MTB/Rif assay

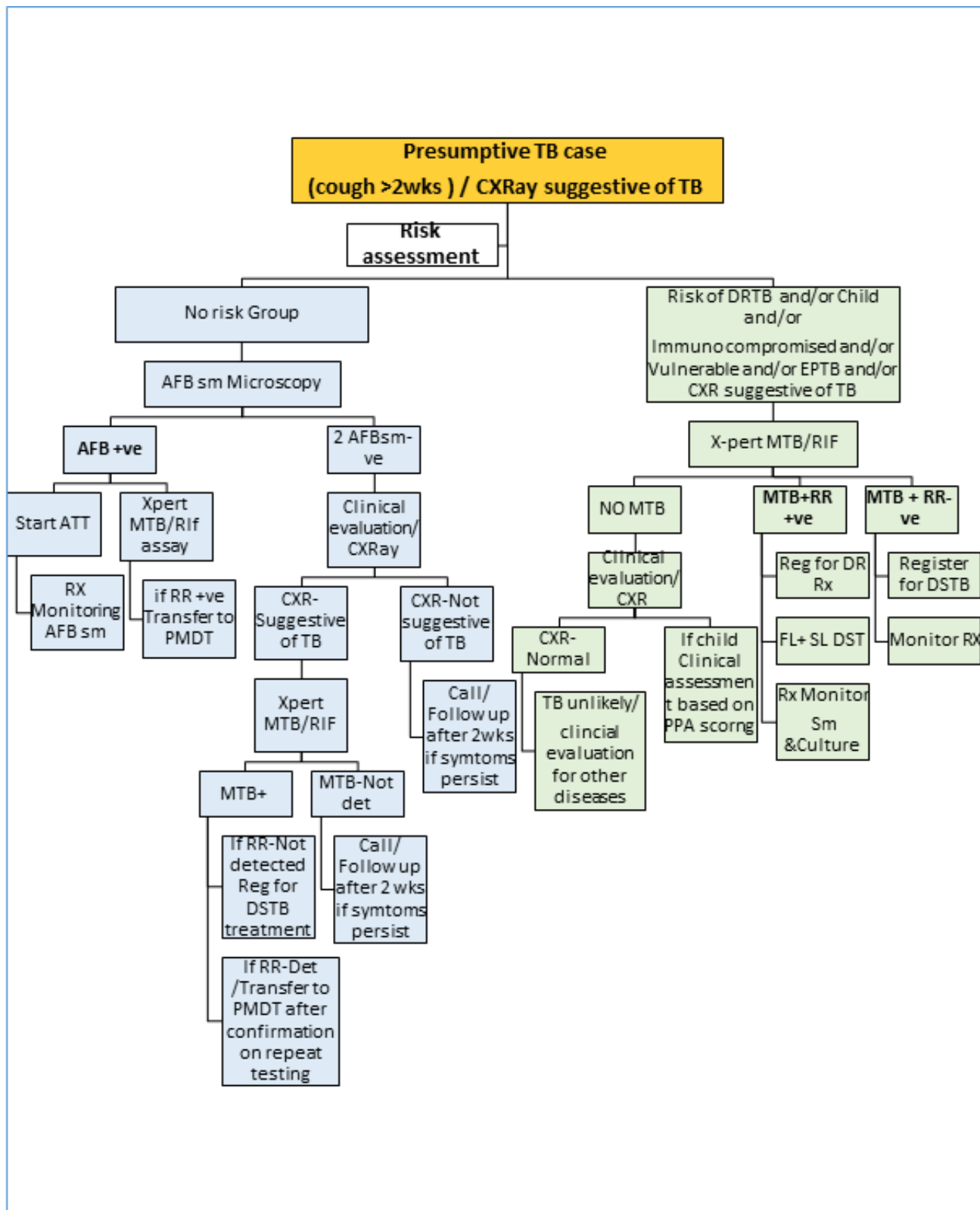
One specimen is recommended for testing. This recommendation applies also to the use of X-pert MTB/RIF

- in processed and unprocessed sputum specimens.
- to gastric lavage and aspirates
- EPTB specimen

Note:

- For all patients group where X-pert /MTB rif assay is recommended as preferred tool, it is recommended that for facilities where X-pert testing is not available on site and specimen requires transportation to higher level laboratory, smear microscopy should be performed in local laboratory and same specimen transported to X-pert site. While X-pert results are awaited, patient should be managed based on microscopy results /clinical diagnosis.
- In situation where xpert MTB/Rif assay is performed as follow on to microscopy, Xpert MTB/RIF assay can be performed on one of the specimen used for microscopy.
- **Diagnosis in Children:** X-pert MTB/RIF is recommended as initial test in all children suspected of having tuberculosis but those with a single X-pert MTB/RIF negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an X-pert MTB/RIF result is negative or if the test is not available

Figure-6: Flow diagram for diagnosis of pulmonary tuberculosis



Consideration for Diagnosis of Extra-Pulmonary Tuberculosis

a) Diagnosis of tuberculosis meningitis

Depending on the organ involved, diagnosis of extra-pulmonary tuberculosis can only be made based on positive X-pert/MTB. AFB smear or mycobacterium (MTB) culture or cytological/histological finding consistent with tuberculosis (caseating granulomas) and/or clinical/radiological evidence of active extra-pulmonary tuberculosis.

It is recommended that X-pert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children (and adults) suspected of having TB meningitis

For CSF specimens, if the sample volume is low, X-pert MTB/RIF should be preferentially used over culture, in order to reach quick diagnosis. If sufficient volume of material is available, concentration methods should be used to increase yield

b) Extra-pulmonary TB at other sites

X-pert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from patient (adults +children) suspected of having extra-pulmonary TB.

- Patient (adults and Children) suspected of having extra-pulmonary TB but with a single X-pert MTB/ RIF-negative result should undergo further diagnostic testing, and those with high clinical suspicion for TB should be treated even if an X-pert MTB/RIF result is negative or if the test is not available.
- Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB, using any method. A pleural biopsy is the preferred sample. The sensitivity of X-pert MTB/RIF in pleural fluid is very low. Nevertheless, any positive X-pert MTB/ RIF result based on pleural fluid should be treated for pleural TB, while those with a negative X-pert MTB/RIF result should be followed by other tests.
- These recommendations do not apply to stool, urine or blood, given the lack of data on the utility of X-pert MTB/ RIF on these specimens

c) Other test for diagnosis of Extra-pulmonary specimen

Number of bacilli in EPTB specimen (tissue, biopsy, pus, urine) is much lower compared to sputum, as a result diagnostic yield of AFB smear is also low in extra-pulmonary specimen. However, AFB microscopy should be attempted for diagnosis of TB in clinical specimen in situation where access to more sensitive diagnostic tools is not available.

Consideration for systematic screening for active Tuberculosis

The primary objective of screening for active TB is to ensure that TB is detected early and treatment is initiated promptly, with the ultimate aim of reducing the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB, as well as helping to reduce TB transmission.

However, while the systematic reviews show that there is some evidence that screening can improve the early detection of TB, the direct evidence remains weak for the impact of screening on health outcomes and TB transmission when compared with passive case-finding alone. Furthermore, data are lacking on the cost effectiveness of screening compared with other interventions to improve early detection, and it is clear that indiscriminate screening can require a lot of resources and is therefore NOT recommended. Decisions on when and how to screen for active TB, which risk groups to prioritize and which algorithm to be used for screening and diagnosis would depend on the epidemiological situation, the capacity of the health system, and the availability of resources.

Key principles for systematic screening for active TB

The following key principles should be considered when planning a TB screening initiative:

1. Before screening is initiated, high-quality TB diagnosis, treatment, care, management and support for patients should be in place, and there should be the capacity to scale these up further to match the anticipated rise in case detection that may occur as a result of screening.
2. **Indiscriminate mass screening should be avoided.** The prioritization of risk groups for screening should be based on assessments made for each risk group.
3. The choice of algorithm for screening and diagnosis should be based on an assessment of the accuracy of the algorithm for each risk group considered, as well as the availability, feasibility and cost of the tests.
4. TB screening should follow established ethical principles for screening for infectious diseases, observe human rights, and be designed to minimize the risk of discomfort, pain, stigma and discrimination.
5. The TB screening approach should be developed and implemented in a way that optimizes synergies with the delivery of other health services and social services.
6. A screening strategy should be monitored and reassessed continually to inform re-prioritization of risk groups, re-adaptation of screening approaches when necessary and discontinuation of screening at an appropriate time.

Recommendations on risk groups to screen

NTP will follow the seven recommendations of WHO, on prioritizing risk groups for screening including three strong and four conditional recommendations.

Three strong recommendation

1. Household and other close contacts of bacteriologically confirmed TB patients
2. People living with HIV at each visit to health facility
3. Current and former workers in workplaces with silica exposure.

Four conditional recommendation

4. Prisons and other penitentiary institutions
5. People with an untreated fibrotic chest X-ray lesion
6. People who are seeking health care or who are in health care and who belong to selected risk groups (underweight, old age, diabetics, COPD)
7. Subpopulations that have very poor access to health care, such as people living in urban slums, homeless people, people living in remote areas with poor access to health care, and other vulnerable or marginalized groups including some indigenous populations, migrants and refugees.

Algorithms for screening and diagnosis

The algorithms have different costs, and requirements in terms of human resources and health systems. The choice of algorithm for screening and diagnosis depends on the risk group, the prevalence of TB, the availability of resources and feasibility.

Subject to availability of resources, different screening options can be used:

- a) Symptoms screening (cough >2 weeks, or
- b) cough of any duration with hemoptysis, weight loss, fever or night sweats.
- c) Chest X-Ray screening.

If symptom screening is used initially, then chest radiography can be used as a second option to improve the pretest probability of the subsequent diagnostic test, and to reduce the number of people who need to undergo further diagnostic evaluation.

Chapter-8 Tuberculosis Treatment

Objective of treatment

Treatment of tuberculosis is focused on both curing the individual patient and minimizing the transmission of *Mycobacterium tuberculosis* to other persons, thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides.

The objectives of tuberculosis therapy are

1. to rapidly reduce the number of actively growing bacilli in the patient, thereby decreasing severity of the disease, halting transmission of *M. tuberculosis* & preventing death;
2. to eradicate populations of persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy; and
3. to prevent acquisition of drug resistance during therapy.

It is very important that people who have TB disease are treated, finish the medicine, and take the drugs exactly as prescribed. If they stop taking the drugs too soon, they can become sick again; if they do not take the drugs correctly, the TB bacteria that are still alive may become resistant to those drugs. TB that is resistant to drugs is harder and more expensive to treat.

Following is the responsibility of provincial /district health management:

- **Universal DST:** All bacteriologically confirmed should be universally tested for rifampicin susceptibility before /at start of treatment. Bacteriologically confirmed TB patient diagnosed on Xpert will simultaneously have Rifampicin results. If patients are diagnosed on AFB microscopy the specimen should be referred for Xpert testing for Rifampicin susceptibility. Rifampicin testing at start of treatment ensure that patients is prescribed effective treatment.
- **Uninterrupted availability of TB drugs:** It is the responsibility of the health facilities registering TB case to ensure uninterrupted availability of free of cost quality assured ATT drugs for complete course of TB treatment for every TB patient.
- **Quality assurance of anti TB drugs:** The quality of anti-Tuberculosis drugs should be ensured through regular and random testing of batches of drugs after procurement during entire shelf life of drugs when drugs are stored in province, district and local health facility stores.
- **Use of First line TB drugs for other disease:** The use of Rifampicin, for diseases other than mycobacterial diseases, should be restricted or limited to very carefully considered indications.

8.1 First Line TB Drugs and treatment regimens

The four essential first line anti-TB drugs (FLD) used in the treatment of Tuberculosis are; Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E). First line drugs are prescribed for treatment of drug susceptible TB (DSTB) case. Standard First line treatment regimen is not effective for treatment of RR and MDR cases and results in unfavorable treatment outcomes. It is therefore important that DST using WHO- recommended rapid tests should be performed for all TB patients prior to starting therapy, including new patients and patients who require treatment.

Prescribing standardized drug regimen for drug susceptible TB is the responsibility of the clinician at the TB care facility. All patients with RR should be registered in TB register and referred/ transferred out to DRTB treatment site for second line treatment.

General guidance for TB treatment

- **Combination antimicrobial therapy:** Large bacterial populations contain a small proportion of naturally resistant mutant (10^{-6} to 10^{-8}) that are resistant to any particular anti-TB drug. When 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 bacterial population is exposed to combination four anti TB drugs the majority of bacterial population including mutant bacilli is killed.

Thus, TB patients are given combination of four drug during initial phase for initial two months and subsequently, are treated with 2-3 drugs phase, during the continuation phase.

- **Fixed dose combination (FDC) drugs:** Evidence has shown that FDCs are non-inferior and as effective as separate formulations of anti-TB agents in terms of treatment failure, death, and treatment adherence and adverse. The standardized fixed dose combination (FDC) treatment of TB is recommended to avoid under treatment, acquired drug resistance, side effect of over-treatment and to maximize cost-effective use of resources. The Fixed dose combination also have other advantages over individualized prescription of drugs e.g. it reduces errors in prescription thereby reducing the risk of development of drug resistance, facilitates estimation & supply of drug requirements. Separate drugs can be prescribed in special conditions. (Refer Chapter-12)
- **Weight based drug dosages:** The tubercle bacilli are killed only when anti TB drugs are given in correct dosages according to body weight to attain appropriate level of bioavailability. Under-dosage leads to drug resistance.
- **Dosing and preferred time for Anti TB drugs intake:** Anti TB medication should be taken in single daily dose in the morning. The absorption of anti-TB drugs is best if taken empty stomach and should be preferred.
- **TB treatment Regimen and duration:** The bacteria grow at different rates and intervals in bacterial population. However, studies have proven that 6months treatment is adequate and there are minimal chances of relapse. TB treatment regimen consists of two phases – the initial and continuation phases.
- **TB treatment prescription coding:** The standard code for anti-TB treatment regimens uses an abbreviation for each anti-TB drug: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). The number at the front of each phase represents the duration of that phase in months. Example, 2HRZE: Duration of this phase is 2 months and drug treatment is daily (no subscript numbers after the abbreviations) with isoniazid, rifampicin and pyrazinamide.
- **Patient support and care:** Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment
- **Directly Observed Treatment:** Directly Observed treatment (DOT) is required for entire duration of treatment in both New and Previously treated cases to avoid the risk of drug resistance. DOT should be used for ALL patients with TB disease, including children and adolescents. There is no way to accurately predict whether a patient will adhere to treatment without this assistance.

Treatment regimen for New TB cases

The standard 6-month regimen for drug susceptible TB (2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin, denoted as 2HRZE/4HR) is the recommended regimen 1 for new patients and it showed better outcomes than other regimens using first-line anti-TB agents for treating drug-susceptible TB.

- **Initial Phase:** During the initial phase a combination of four drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol “HRZE”) are administered for a period of two months (sixty doses).
- **Continuation phase:** During continuation phase isoniazid and rifampicin (HR) are administered daily for four months.

All New bacteriologically confirmed TB patients should be tested for rifampicin resistance (RR) before/at start of TB treatment. All New TB patients including B+ve/ Rif Sensitive (RS) and clinical diagnosed are enrolled on first line TB treatment (treatment for new case). The treatment is given in two phases, the initial & continuation phase

Treatment regimen for previously treated TB cases

WHO has recently revised and/or updated its guideline with regard to empiric Cat-II treatment (2017), which recommends that the category II regimen should no longer be prescribed and DST should be conducted to inform the choice of treatment

regimen.

In TB symptomatic patients with history of previous TB treatment, every effort should be made for the bacteriological confirmation of Tuberculosis especially in those with pulmonary lesions. As all TB patients with history of previous TB treatment are at increased risk of drug resistance, rifampicin testing should be ensured for all previously treated TB cases before start of treatment and first line treatment should be prescribed only if RR is excluded after testing.

TB diagnosis without bacteriological confirmation should be limited to those PTB and EPTB cases in whom collection of specimen is not possible and there is a strong clinical evidence of active TB.

Preferably clinically diagnosed previously treated PTB cases should not be more than 5% of all notified previously treated PTB cases.

Previously treated TB

- All previously treated TB cases B+/Rifampicin susceptible: This group of patient are at higher risk of drug resistance, Fresh specimen from all these patients should be referred for comprehensive DST.
Regimen: Patient should be started on empiric treatment for previously treated case and treatment adjusted based on DST results (if Poly or mono drug resistance).
- **Initial Phase:** During the initial phase Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, (HRZE) are given for the first two months.
- **Continuation phase:** During the continuation phase, Isoniazid, Rifampicin, and Ethambutol (HR) are administered daily for four months under observation.

Sr.	Patient Category	Initial	Continuation
1	New TB case B + & B - (Regimen 1)	2HRZE	4HR
2	Clinically diagnosed previously treated cases	2HRZE	4HR
3	Bacteriologically confirmed previously treated cases with INH resistance (laboratory confirmed) and FQ resistance (laboratory confirmed) or FQ status unknown (Regimen 3)	6HRZE	
4	Bacteriologically confirmed previously treated cases with INH resistance and FQ sensitive (laboratory confirmed) (Regimen 3) Enrolled as new patient	6HRZE + LFx	

Clinically diagnosed previously treated EPTB patients

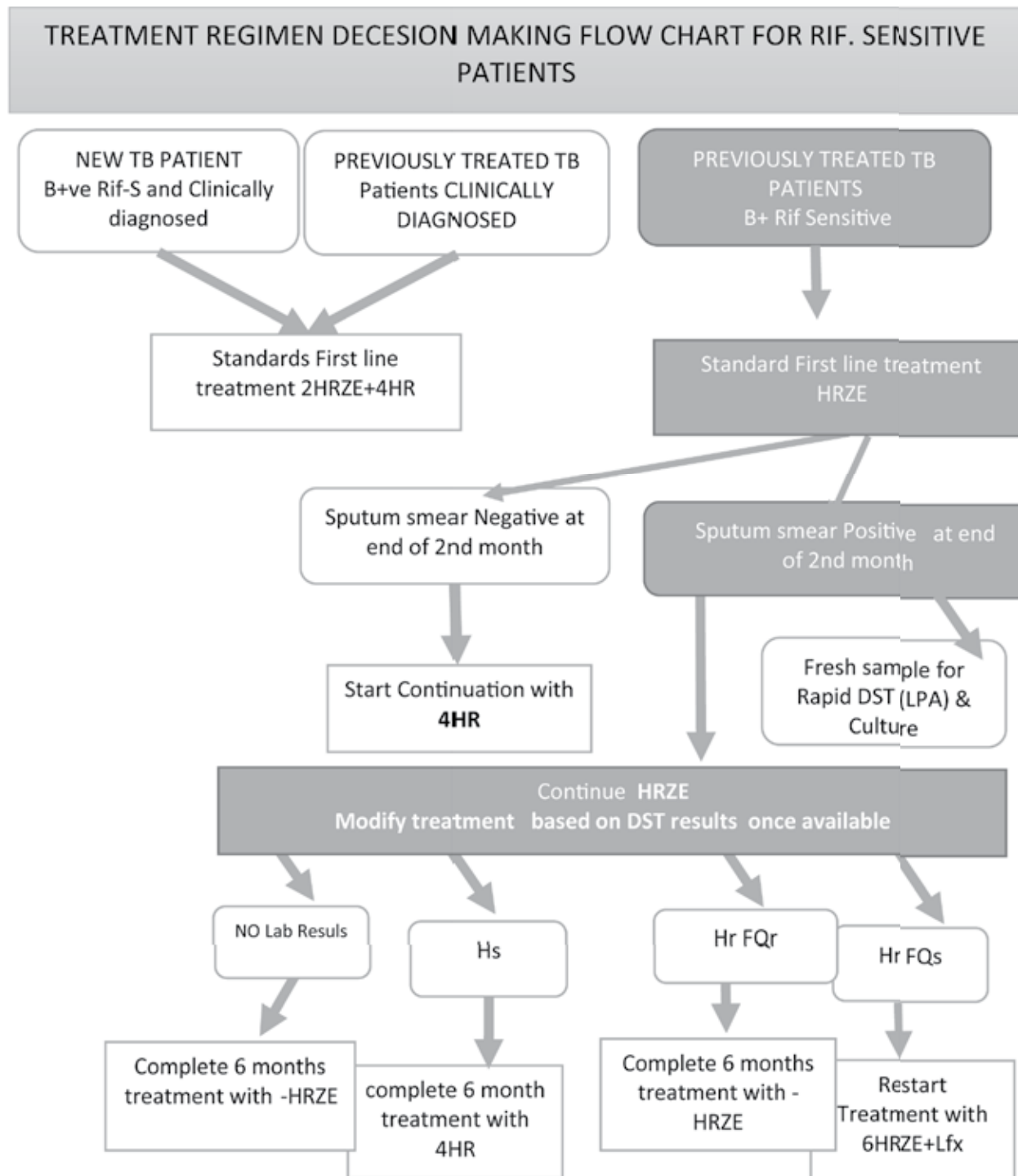
Patient should be treated based on disease site and clinical evidence of the disease.

Rifampicin sensitive - Isoniazid resistant TB case:

Patients with Rifampicin sensitive and only INH resistant will be treated with HRZE for six months if resistance to FQ or FQ status unknown

Patients with Rifampicin sensitive and only INH resistant will be treated with HRZE + Levofloxacin for six months if sensitive to FQ

Note: All previously treated TB patients who are clinically diagnosed will be treated as "NEW TB CASE"
All TB patients on Rifampicin need administration of drugs under direct supervision



Note:

1. All B+ve should be tested for Rif at start of treatment
2. All TB patients B+ Rif -sensitive and clinically diagnosed shall be started on standard First line treatment (Streptomycin will no longer be used)
3. *Where feasible and easily accessible, refer / send sample for H -DST at start of treatment for patients at higher risk of H resistance e.g. previously treated TB cases after failure and lost to follow up and modify treatment once DST results are available
4. Send samples for H- DST for all previously treated TB patients who remain/are AFB smear positive at end of 2nd month of treatment
5. For all previously treated TB patients who are /remain AFB smear positive at the end of two-month treatment continue treatment with RHZE
6. Specimens from all TB patients who are reported H-resistant should first be tested for FQ resistance
7. Patient reported having Hr FQs -TB shall be given a full course of treatment with 6HRZE+Lfx

Chapter-8A Tuberculosis Treatment in Adults

Dosage and duration of Treatment

The dosages & duration of fixed dose combination and individual drugs for each category of treatment are given in the tables below:

Table-8: New cases and previously treated cases regimen and fixed-dose combinations dosages in adults

		Duration	Weight band (kg)/ based FDC drug dose (Tablets)		
			30-39	40-54	55 & >
NEW	New TB and B+ and CD Previously treated TB cases				
Initial Phase	HRZE (H 75mg + R 150mg + Z 400mg + E 275mg)	2month	2	3	4
Continuation Phase	HR (H 75mg + R 150mg)	4month	2	3	4
Clinically diagnosed previously treated cases	HR* (H 150mg + R 300mg)	4month	1	1.5	2
Previously treated TB Cases	All B+/Rif sensitive Previously treated TB cases				
Bacteriologically confirmed previously treated cases with INH resistance (laboratory confirmed) and FQ resistance (laboratory confirmed) or FQ status unknown					
Initial Phase	HRZE (H 75mg + R 150 mg + Z 400mg + E 275mg)	2 month	2	3	4
Continuation Phase	HRZE (H 75mg + R 150mg + Z 400mg + E 275mg)	4month	2	3	4
Bacteriologically confirmed previously treated cases with INH resistance and FQ sensitive (laboratory confirmed)					
		6HRZE+ LFx	2	2	3

*(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+ Levofloxacin 250 mgs)

Note: Anti-TB drugs may need to be temporarily suspended or stopped in case of severe drug intolerance or toxicity prolonging treatment beyond the recommended period of 6 months has minimal benefits provided the patient has taken the medication without interruption. Except for situation mentioned below.

Duration of treatment in EP TB

Site of EP	Regimen	Total duration
Cervical lymph node & pleural effusion	2 HRZE / 4 HR	6 months
TB meningitis	2 HRZE / 10 HR	12 months
Other forms of EP	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 (Strong recommendation, moderate certainty in the evidence).
- In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence).

Managing patients who interrupt treatment and Treatment Outcomes

Review the Record of Previous Treatment: Management of patients after treatment interruption is based on review of information about treatment before interruption and current smear results and Xpert results of the patient. Record of the previous treatment (before interruption) is important to know:

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

Table-9: Management of New TB patients with Interrupted Treatment

Length of interruption	Do a smear?	Result of smear	Do Xpert?	Result Xpert	Register again as	Treatment
Length of treatment			<1 month			
<2 weeks	No	-	No	-	-	Continue on same treatment for new case
2-8 weeks	No	-	No	-	-	Start again on treatment for new case
>8 weeks	Yes	Positive	Yes	MTB+RR-MTB+RR+	*Treatment after lost to follow-up	Start on treatment for new case If RR+ Transfer to PMDT
		Negative	Yes	MTB+RR-MTB+RR+ MTB ND	*Treatment after lost to follow-up	Start on treatment for new case If RR+ Transfer to PMDT Send for culture & wait for result
Length of treatment			>1 month			
<2 weeks	No	-	No	-	-	Continue on same treatment for new case
2-8 weeks	Yes	Positive	Yes	MTB+RR-MTB+RR+		Start again on same treatment for new case If RR+ Transfer to PMDT
		Negative	Yes	MTB+RR-MTB+RR+ MTB ND		Start again on same treatment for new case, If RR+ Transfer to PMDT Send for Culture, Send for culture,& wait for result
>8 weeks	Yes	Positive	Yes	MTB+RR-MTB+RR+	*Treatment after lost to follow-up	Start on Previously treated regimen case & send sample for DST If RR+ Transfer to PMDT
		Negative	Yes	MTB+RR-MTB+RR+ MTB ND	*Treatment after lost to follow-up	Start on Re-treatment regimen & send sample for DST If RR+ Transfer to PMDT Send for culture,& wait for result

Table-10: Management of Previously Treated TB Patients with Interrupted Treatment

Length of interruption	Do a smear?	Result of smear	Do Xpert?	Result Xpert	Treatment
Any length of treatment					
<2 weeks	No	-	No	-	Continue on “Previously treated regimen”
2-8 weeks	Yes	Positive	Yes	MTB+RR- MTB+RR+	Start again treatment at “Previously treated regimen” If RR+ Transfer to PMDT
		Negative	Yes	MTB+RR- MTB+RR+	Start again treatment for “Previously treated regimen” If RR+ Transfer to PMDT
>8 weeks	Yes	Positive	Yes	MTB+RR- MTB+RR+	Register as Treatment after lost to follow up and start treatment for “Previously treated regimen” and send sample for DST If RR+ Transfer to PMDT
		Negative	Yes	MTB+RR- MTB+RR+ MTB ND	Register as Treatment after lost to follow up and start treatment for “Previously treated regimen” and send sample for DST If RR+ Transfer to PMDT Send for culture,& wait for result

Chapter-8B Tuberculosis Treatment in Children

Principles of treatment of TB in children are same as for adults. Children with TB usually respond well with symptomatic improvement during initial phase and good outcome.

Dosages are calculated according to weight (not age) TB drugs are very well tolerated in almost all children and the most important adverse event is hepatotoxicity.

Register all children receiving anti-TB treatment. Weight is important for monitoring treatment response. Treatment outcomes should be reported

Dosage and duration of treatment

The section below has been adapted from the recent WHO childhood TB guidelines 2014. For children above 25Kgs weight adult dosages and preparations can be used

Table-11: Recommended daily dose for 1st line anti-TB drugs for children up to 25 kg

First Anti TB drugs	Dose and range (mg/kg body weight)	Maximum dose (mg)	Remarks
Isoniazid(H)	10 (7-15)*	300	The higher end of the range of isoniazid dose applies to young children; as the children grow older the lower end of the dosing range becomes more appropriate
Rifampicin(R)	15 (10-20)	600	
Pyrazinamide (Z)	35 (30-40)	-	
Ethambutol(E)	20 (15-25)	-	Ethambutol can be safely used at recommended dosages in all ages.

The higher end of the range of isoniazid dose applies to young children; as the children grow older, the lower end of the dosing range becomes more appropriate.

Table-12: Recommended treatment regimens for TB in children

	TB diagnostic type	Anti-TB drug regimens ^a	
		Initial phase	Continuation phase
	Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings ^b		
PTB	Smear negative pulmonary TB Intrathoracic lymph node TB	2HRZ	4HR
EPTB	Tuberculosis peripheral lymphadenitis		
PTB	Extensive pulmonary disease (define extensive) Smear-positive pulmonary TB	2HRZE**	4HR (months to reconfirm)
EPTB	Severe forms of extra-pulmonary TB (other than tuberculous meningitis/ osteoarticular TB)		
EPTB	Tuberculous meningitis* and osteoarticular TB	2HRZE**	10HR

*The decision on the regimen for a child with tuberculous meningitis should be made by an experienced clinician. It is suggested that the patient be treated in a hospital.

**For children under 5 Kg, Ethambutol usage should be limited to recommendation by the pediatrician under special circumstances. For children over 5 Kg, regular visual acuity and red-green discrimination checks should be arranging and drug should be stopped in case of any change.

Table-13: Weight band table using widely available dispersible FDC

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

The use of childhood TB medicines is critical, as there is greater understanding that crushing adult tablets for children may result in incorrect dosages.

See “Definitions and distinctions” section for discussion of WHO definitions of high and low prevalence of HIV and isoniazid resistance.

New Pediatric Fixed Dose Combination Drugs

The need for childhood TB medicines has been critical in recent years as there is greater understanding that crushing adult tablets for children may result in incorrect dosages. This raises question of efficacy of treatment and the subsequent threat of drug resistance. The previously used drug formulation in dispersible FDCs were also not in line with the dosages recommended for childhood cases, with calculations required to estimate the correct dosage.

Accordingly, the new FDC’s have been developed to ensure proper dosing of childhood cases. It is important to note that the dosage parameters (by weight) as given in WHO 2014 guidance document remains the same; the formulation of the associated FDCs have been changed. Some information about the new FDCs is given below in Table 12.

Table-14: New Pediatric Fixed Dose Combination Drugs Profile

Product	<ul style="list-style-type: none"> Isoniazid 50 mg, Rifampicin 75mg, Pyrazinamide 150mg (2 months’ initial phase) Isoniazid 50 mg, Rifampicin 75mg, (4 months continuation phase)
Formulation	<ul style="list-style-type: none"> Tablets come in palatable fruit flavors Tablets are dispersible in 10 seconds, to be mixed in 50 ml of water Once reconstituted the dispersible should be drunk in 10 minutes
Training needs	<ul style="list-style-type: none"> Designed to be easy to use and allow the WHO recommended dose without crushing and chopping Minimum training needs for providers including parents to administer
Administration	<ul style="list-style-type: none"> FDC to be dissolve in 50 ml of water and child should consume the complete fluid within 10 second of dissolving to be taken on an empty stomach.

Pakistan Pediatric Association Scoring Chart

Table-15: Pakistan Pediatric Association Scoring Chart (REVISED 2016)

	1	2	3	4	5
Age	< 5 years				
Close Contact*	TB suggestive	B –ve (Clinically diagnosed TB)	B+ve (Bacteriological positive)		
PEM/SAM**	Yes	Not responding to Nutritional rehabilitation for 02 months			
H/O Measles, Whooping Cough	3-6 months	< 3 months			
HIV		Yes			
Immuno-compromised ***	Yes				
Clinical Manifestation ****		Suggestive		Strongly suggestive	
Radio Diagnostic imaging *****	Non-specific	Suggestive of TB	Strongly suggestive		
Tuberculin Skin /PPD testing	5-10 mm		> 10mm		
Xpert test					Positive for TB
Granuloma	Non specific				Positive for TB

INTERPRETATION

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)

Description of Condition to be assessed for diagnosing Childhood TB (Revised PPA Scoring chart 2016)

* Close contact	<p>History of cough for more than 2 weeks among the house hold of child (score 1), contact tracing is required</p> <p>B-ve TB patients among the house holds (score 2), may or may not be receiving/completed anti tuberculous treatment</p> <p>B+ve TB patient among the house holds (score 3). May or may not be receiving/completed anti tuberculous treatment</p>
**PEM/SAM	<p>(Protein Energy Malnutrition/Severe acute malnutrition) Use WHO Recommended Z. scoring chart (1)</p> <p>Not responding to Nutritional rehabilitation for 02 months (2)</p>
*** Immunocompromised status	<p>Malignancies like leukemia or lymphomas etc.</p> <p>Immunodeficiency diseases like agammaglobunemia etc. Chemotherapy /Immuno- suppressive therapy such as steroids for more than 2 weeks.</p>
**** Clinical Manifestation	<p>Suggestive of TB:</p> <p>Pulmonary Findings (unilateral wheeze, dullness), weight loss, Hepato- splenomegaly, Lymphadenopathy, ascites etc.</p> <p>Strongly suggestive of TB:</p> <p>Matted lymph nodes, abdominal mass or doughy abdomen, sinus formation, gibbous formation, chronic mono arthritis, meningeal findings (bulging fontanel, irritability, choroid tubercle, papilledema)</p>
*****Radio-Diagnostic/ imaging studies includes Chest X-ray, CT Chest/MRI etc.	<p>Non-specific Ill-defined opacity or patchy infiltrates on chest X-Ray, marked broncho-vacular marking.</p> <p>Suggestive of TB:</p> <p>Consolidation not responding to antibiotic therapy, Para-tracheal, or mediastinal lymphadenopathy,</p> <p>Strongly suggestive:</p> <p>_Miliary Mottling, cavitation, Tuberculoma on CAT scan/MRI brain, collapse vertebrae etc.</p>

Introduction

In line with the End TB Strategy, TB/HIV collaborative activities are fully including in NTP policy to prevent and control TB in Pakistan.

It is well known that persons who are infected with HIV, irrespective of their age, have much higher risk of developing TB than those who are not. This risk is estimated at 20 to 37 times higher. TB is one of the leading causes of death in PLHIV and is associated with an excess in mortality in TB patients who are HIV-infected in comparison to those who are not. PLHIV are more likely to develop smear-negative pulmonary TB and EPTB than HIV-negative persons. This is likely to contribute to a delay in establishing the diagnosis of TB, and subsequently to an excess in deaths among PLHIV.

With an estimated prevalence rate of less than 0.1%, Pakistan continues to have a low-level HIV epidemic among general population however, serial surveillance results indicate that concentrated epidemics have already established among key populations (KPs). As in several other regions, the HIV epidemic in Pakistan is characterized by high initial prevalence among injecting drug users (PWID), which has already expanded to Transgender /Transgender Sex Workers (TGs) with the potential to expand into female sex workers (FSWs). Pakistan faces a concentrated but a severe HIV epidemic among PWIDs, which first manifested in an outbreak of HIV among PWIDs in Larkana. Since then, surveillance data shows that HIV is getting well established in PWIDs throughout the country and despite various preventive efforts, the infection rates among PWIDs steadily increased to 37.8% (37.3% to 38.3%) in 2011. Not only has the overall prevalence increased, but the number of sites with relatively advanced epidemics has also expanded. Of concern is the growing increase in the HIV prevalence among Transgender and Male sex workers, which stood at 7.2% (6.8% to 7.5%) and 3.1% (2.8% to 3.4%) respectively according to the last National surveillance round of IBBS.

The existing sentinel surveillance system has indicated that the prevalence of HIV infection among TB patients was 0.4 percent in 2017. Although Pakistan is a low HIV prevalence country, there are estimated 150,000 people living with HIV (PLHIV) and are at high risk of being affected with TB.

The NTP Pakistan working together with AIDS control Programme has established National TB/HIV Collaborating Board, and provincial level TB/HIV coordination committees, which have been constituted in the four provinces.

Strengthening mechanisms for delivering integrated TB/HIV services

(1) Maintaining and strengthening the existing coordination mechanism for collaborative TB/HIV activities. There is a Coordination Committee for Collaborative TB/HIV Activities operating at national level in Pakistan. This committee includes the NTP, NACP and the relevant key stakeholders which are dealing with TB and/or HIV. Its role is to:

- Provide the general policy on TB/HIV collaborative activities;
- Design strategic directions from time to time
- contribute to planning TB/HIV interventions and activities;
- help in assessing progress made in implementing TB/HIV activities and evaluating their outcomes and impact;
- ensure consistent and coherent communications with partners and decision makers about TB and HIV;

- ensure the involvement of civil society, NGOs, CSOs and community organizations.

The sub-coordination committees for collaborative TB/HIV activities established in the Provinces of Punjab, Sindh, KPK and Balochistan they must collaborate with the coordination committee which operates at national level. Each sub-coordination committee will meet every six months to discuss the progress made in the implementation of interventions, the strategic orientations, the issues related to the coordination between NTP and NACP and the actions that need to be taken. The sub-coordination committees will also meet on ad hoc basis.

(2) Ensuring the surveillance of HIV infection among TB patients and TB among PLHIV. Sound data on HIV infection among TB patients and TB among PLHIV are essential for planning and implementation of the interventions and activities defined by NTP and NACP.

NTP must collaborate and support NACP to establish and update appropriate information on both diseases through the existing routine information systems of the two programs and whenever needed through surveys and relevant sentinel surveillance systems.

(3) Undertaking joint TB/HIV planning to integrate TB and HIV services. The implementation of joint TB/HIV collaborative activities must be planned with both the NTP and NACP to avoid unnecessary duplication of efforts. Both programs must together establish a joint training agenda and plan on joint collaborative TB/HIV activities targeting the relevant categories of health workers.

The expansion of the interventions of both programs must be coordinated by the central units of NTP and NACP in order to ensure effective implementation of joint collaborative TB/HIV activities.

Both programs must use coherent and consistent messages in their communication with national and international stakeholders and decision makers, in line with the approach established by the Coordination Committee for Collaborative TB/HIV Activities.

(4) Monitoring and evaluating collaborative TB/HIV activities. The NTP is using the WHO-recommended recording and reporting system in which HIV data on TB patients are included. However, to have full information on TB/HIV activities, NTP must have access to the information generated by the monitoring and evaluation system for HIV Care/ARV treatment established by the NACP. Both programs must collaborate to exchange information and jointly monitor and evaluate collaborative TB/HIV activities.

Reducing the burden of TB among PLHIV

Intensifying TB case-finding and ensuring high-quality anti-TB treatment TB screening in PLHIV. The NACP has adopted the internationally recommended clinical algorithm to screen PLHIV for TB if the patient is reporting one of the following symptoms:

- cough (of any duration)
- fever
- weight loss or
- night sweats.

To this end, the NTP staff should support the NACP to enhance the capacity building of the staff practicing in HIV and AIDS health facilities as well as the community workers of NGOs involved in HIV and AIDS issues in communities. This capacity building should focus on TB screening and TB management in PLHIV and people at high risk of HIV infection. Any PLHIV who has one of these symptoms must be clinically evaluated for TB in the closest BMU, including using CXR and/or Xpert testing whenever needed.

- **TB Diagnosis in PLHIV.** All the PLHIV who were screened positive with the clinical algorithm must:
 - have Xpert MTB/RIF testing and

- be checked for any danger signs, such as incapacity to walk unaided, respiratory rate > 30 per minute, fever > 39°, or pulse rate > 120 per minute.

If there is one or more of the danger signs, then the clinical context should be considered as severe and the patient must be immediately referred to hospital for appropriate management;

If there is no danger sign, then there is no need for immediate hospitalization and the results of Xpert testing need to be used as follows:

- If the Xpert test is positive for MTB and:
 - if it does not show any rifampicin resistance then the PLHIV will be treated and managed for active TB in line with the NTP guidelines;
 - if it shows a rifampicin resistance then the patient must be urgently referred to the relevant health facility for appropriate management in line with the NTP guidelines on PMDT.
- If the Xpert test is negative for MTB, then CXR must be performed for the patient and a further clinical assessment and actions (such as provision of antibiotic) need to be undertaken to consider or rule out the diagnosis of active TB.

It is important to highlight that EPTB is more common in PLHIV than in HIV-negative patient. The commonest forms are pleural effusion and lymphadenopathy TB; severe forms of EPTB may be observed, such as pericardial, meningeal, haematogenous (disseminated or Miliary) TB.

In addition, children living with HIV who have any of the following symptoms: poor weight gain, fever, current cough or contact history with a TB case, may have TB and should be evaluated for this disease and other conditions. If the evaluation shows no active TB, children should be offered IPT regardless of their age.

All PLHIV who are diagnosed with active TB must be treated with the standardized regimen NTP (2HRZE/4HR) and monitored in line with the national guidelines.

(2) Isoniazid preventive therapy. There is strong evidence that IPT is effective in reducing the incidence of TB and death from TB in PLHIV. The provision of IPT to PLHIV does not increase the risk of developing isoniazid-resistant TB.

Adults and adolescents living with HIV, who have none of the following symptoms: cough, fever, weight loss or night

- sweats, are unlikely to have active TB and should be treated with IPT. Isoniazid needs to be given for 6 months (5mg/kg/ day) as part of a comprehensive package of HIV care for all eligible PLHIV irrespective of the degree of immunosuppression, ARV use, previous TB treatment and pregnancy.
- Providing IPT as a core component of HIV preventive care should be the responsibility of NACP and HIV and AIDS service providers.
- Children living with HIV, aged more than 12 months, who do not have poor weight gain, fever nor cough and no contact with a TB case should receive 6 months of IPT (10mg/kg/day) as part of a comprehensive package of HIV prevention and care services.
- Children living with HIV, aged less than 12 months, who have contact with a TB case and in whom systematic screening and evaluation did not show any active TB should receive 6 months IPT (10mg/kg/day).
- In addition, all children living with HIV after successful completion of treatment for TB disease should receive isoniazid for an additional 6 months.

(3) TB infection control in health care facilities. Staff, working in health facilities providing HIV services, should prioritize, during the triage, the identification of patients with symptoms compatible with TB, quickly proceed to their TB assessment with the relevant BMU in order to promptly treat them if they have active TB.

Infectious TB patients must be separated from the other patients in ambulatory settings and in hospital wards.

Masks must be given to patients with respiratory symptoms and to TB patients when they attend health facilities ensuring HIV services. Appropriate ventilation must be ensured in these health facilities.

HIV-positive health workers who are dealing with TB patients' management should not be involved in undertaking such task and need to be removed to duties others than those associated with TB services.

Further measures to ensure adequate infection control are detailed in the national guidelines' document on TB infection control.

Reducing the burden of HIV in patients with TB

(1) Providing HIV testing and counselling to TB patients. The NTP should make available rapid tests for HIV screening and HIV infection confirmation for patients diagnosed with TB.

HIV testing and counselling must be offered to all TB patients as well as to partners of known HIV-positive TB patients. TB patient who has HIV-negative test, but is potentially exposed to HIV or has a high risk for HIV infection needs to be re-tested after 4 weeks from the time of initial testing.

(2) Introducing HIV prevention interventions for patients with TB. Health workers dealing with co-infected TB/HIV cases in BMUs and other relevant health facilities must coordinate their efforts in treating and managing these patients with the health sites providing HIV care services. They should also provide to their patients appropriate and coherent health education messages and information in line with the policy established by both NTP and NACP.

In addition, health workers of BMUs should refer all HIV-positive pregnant women, with whom they are dealing, to health facilities which provide services for prevention of vertical transmission of HIV. It is worthwhile to note that for HIV-positive pregnant women who do not need ARV treatment for their own health, prophylaxis with ARV medicines is needed to prevent HIV transmission and should be continued until one week after all infant exposure to breast milk has ended.

(3) Providing co-trimoxazole preventive therapy for TB patients living with HIV. Co-trimoxazole preventive therapy must be provided to all TB patients who are HIV-infected, regardless of their CD4 cell count. It should be implemented as an integral component of the HIV care package. Co-trimoxazole is a broad-spectrum antimicrobial agent that prevents a range of secondary bacterial and parasitic infections in PLHIV.

Co-trimoxazole preventive therapy is a simple, well-tolerated and cost-effective intervention which can be administered concomitantly to ARV treatment. It reduces death rate in co-infected TB/HIV patients.

Health workers dealing HIV-infected TB patients in health facilities should coordinate their efforts with health sites providing HIV care in order to ensure co-trimoxazole preventive therapy to these patients.

(4) Providing antiretroviral therapy for TB patients living with HIV. ARV therapy must be provided to all TB patients who are HIV-infected irrespective of their CD4 cell counts. MDR-TB cases who are treated with second-line TB drugs should also receive ARV medicines.

ARV therapy greatly improves the survival and the quality of life of HIV-infected TB patients, prevents HIV transmission and should be considered part of HIV and TB treatment and prevention. TBMs must coordinate their efforts with the most accessible and appropriate health sites providing HIV care to ensure ARV therapy to HIV-infected TB patients.

TB treatment needs to be initiated first, followed by ARV therapy as soon as possible within the first 8 weeks of TB treatment. However, co-infected TB/HIV patients with major immunosuppression (ex.: CD4 count < 50 cells/mm³) should receive ARV therapy immediately within the first 2 weeks of initiating TB treatment. However, caution is needed in HIV-infected patients with TB meningitis since more severe adverse reactions have been observed with immediate ARV therapy when compared with its initiation two months after the start of anti-TB treatment.

Patients should be closely followed-up to monitor and assess the occurrence of:

- Side-effects related to co-treatment and
- TB associated immune reconstitution inflammatory syndrome, which is common in patients with TB started on ARV therapy, but usually self-limited.

(5) Ensuring HIV prevention interventions, treatment and care for TB patients living with HIV. It is crucial that BMUs and HIV care sites joint their efforts to ensure integrated services for prevention, diagnosis, treatment and care of TB and HIV.

The provision of HIV prevention, treatment and care package must be continued for HIV-infected patients who completed their anti-TB treatment.

Children living with HIV: should be evaluated for symptoms of poor weight gain, fever, cough or contact history

with a TB case.

- Those who have any one of these may have TB and should be evaluated for TB (see chapter on Case finding and TB diagnosis) and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age
- Who do not have these symptoms are unlikely to have active TB

HIV testing and counselling (HTC)

HIV testing and counseling (HTC), must adhere to the five Cs—Consent, Confidentiality, Counseling, Correct test results and linkage to Care. Scaling-up of provider initiated testing and counseling (PITC) should be considered in TB clinic located in district with HIV epidemics.

To improve the quality of service delivery and the acceptability and uptake of HTC, for many settings WHO recommends the use of rapid diagnostic tests (RDTs) rather than conventional laboratory based diagnostics such as enzyme immunoassay (EIA). RDTs allow quicker provision of test results and post-test counseling. Most RDTs do not require venipuncture specimen collection, but instead can be performed with simple finger-stick collection procedures.

Pregnancy

- Health workers in charge of TB treatment provision should ask women in childbearing age before initiating the treatment whether they are pregnant. A pregnant woman with TB must be informed that successful treatment with standard regimen is important for successful outcome of pregnancy. All first line TB drugs are safe in pregnancy.
- A pregnant woman with a previously treated TB, must be managed in the same manner as any previously treated TB patient.
- The pregnant TB patients should be counselled and reassured that successful treatment of TB with the recommended standardized regimen is important for successful outcome of pregnancy.
- All pregnant women with TB should receive B6 vitamin (pyridoxine) supplementation during treatment.

Breastfeeding

- Female TB patients who are breastfeeding should receive a full course of TB treatment.
- All anti- tuberculosis drugs are compatible with breastfeeding and woman taking them can safely continue to breastfeed.
- Timely and properly applied chemotherapy is the best to prevent transmission of tubercle bacilli to her baby.
- Mother and child baby 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 the end of Isoniazid prophylaxis if not already vaccinated.

Oral Contraception

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.

TB and Diabetes

Treatment and case management of TB in people with diabetes should be provided in accordance with existing TB treatment guidelines and international standards. The same TB treatment regimen should be prescribed for people with diabetes as for people without diabetes.

However, given the apparent increased vulnerability among people with diabetes, it is essential that all standard aspects of TB treatment and case management be optimized for this group. This includes correctly prescribed treatment regimens, optimal patient support and supervision, diabetes testing, improved glucose control and clinical monitoring as per national guidelines.

Liver diseases

This paragraph covers TB treatment in patients with pre-existing liver disease; for the detection and management of hepatitis induced by anti-TB drugs

A patient with hepatitis virus carriage, positive past history of acute hepatitis and excessive alcohol consumption can receive TB treatment provided she/he has no clinical evidence of chronic liver disease. However, patients with these conditions may develop reactions to anti-TB drugs.

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment. The more unstable or severe the liver disease is; 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 a fluoroquinolone. (suggestion: 2 months' streptomycin (daily) + ethambutol (daily) + fluoroquinolone (daily), then 16 months of ethambutol(daily) + fluoroquinolone (daily) + streptomycin 2 or 3 times a week + ototoxicity monitoring).

Patients with renal failure

TB patients with renal failure or severe renal insufficiency will receive 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. Isoniazid and rifampicin are eliminated by biliary excretion, therefore, there will be no change in dosing of these TB medicines. As there is a significant renal excretion of ethambutol and metabolites of pyrazinamide, these two drugs need to be given three times per week at the following doses: 25 mg/kg/day for pyrazinamide and 15 mg/kg/day for ethambutol. While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy.

Because of an increased risk of nephrotoxicity, streptomycin should be avoided in patients with renal failure.

Epilepsy

Dose of the anticonvulsant drug should be adjusted and the patient should be monitored closely for increasing seizure frequency.

Chapter-9 Supervision and Monitoring TB treatment

All patients should be supervised for treatment intake and monitored to assess their response to therapy (Standard 10 of the ISTC). Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions.

9.1 Directly Observed Treatment (DOT)

Directly Observed treatment (DOT) is required for entire duration of treatment in both New and Previously treated cases to avoid the risk of drug resistance. Regular supervision is required to ensure that the patient takes all the drugs prescribed and every dose of treatment is swallowed under the direct supervision of a treatment supporter. The detailed strategy to observe community-based DOTS at all TB Care Facilities in the country is implemented and its key features are:

- Treatment services should be provided as close to the patient's home as possible
- If any health facility is not near to his/her home, he will select a treatment supporter who will observe the daily intake of drugs at a mutually agreed place.
- The treatment supporter identified by the patient will be briefed by the DOTS facilitator at the TB Care facility of the protocols of observing the intake of drugs.
- The treatment supporter accompanied by patient will collect the drugs on monthly basis from TB Care Facility where patient is registered throughout full course of treatment
- Patients are referred to the TB Care Facility management of adverse reactions if any and for follow-up sputum examinations at the end of months 2, 5 and 6 and the sputum results recorded in TB-01 & TB03.

DOT should be done at a time and place that is convenient for the patient. The following treatment administration options may be offered to patients on TB treatment:

- a) Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment.
- b) DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment
- c) 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.

9.2 Role of counseling and health education in Tuberculosis

Counselling and health education should be provided to the health staff, patients and their relatives/attendants. It is often necessary to carry out such a counselling session for a patient in the presence of treatment supporter who will monitor his/her intake of drugs on a daily basis.

The patient shall be explained the importance of contact screening to bring the household members to get screened. The contact's sputum examination is done with appropriate diagnostic

Health education should be provided on continuous basis during treatment period so that s/he should understand the importance of regular intake of drugs for the complete duration and importance of follow up clinical and lab examination.

9.3 Retrieval of delayed patients

Every effort should be made to educate the patient on the importance of adhering to his/her treatment schedule. If during an initial phase of treatment, a patient misses his/her treatment for more than 2 consecutive days, he/she must be reminded on cell phone/SMS, and in case of no response, shall be traced by health workers or by the treatment supporter.

If during continuation phase of treatment, a patient fails to collect drugs for up to one week after the drug collection day he must be reminded on cell phone/SMS, and in case of no response shall be traced by health workers.

Assessing treatment response in New and Previously Treated Pulmonary TB patients, and acting on the results

Response to treatment in pulmonary TB patients is monitored by sputum smear examination. This recommendation applies both to new patients treated with regimens containing 6 months of rifampicin (2HRZE/4HR) and to previously treated patients receiving the 6-month regimen with first-line drugs (2HRZE/4HR).

See Table-14 for a monitoring scheme with sputum smear microscopy.

New bacteriologically confirmed pulmonary TB patients with positive sputum smears and /or MTB detected on Xpert at the start of treatment. These patients should be monitored by sputum smear microscopy at the end of initial phase and then at the completion of fifth and sixth months of treatment.

New clinically diagnosed pulmonary TB patients whose sputum smear microscopy was negative (or not done) and MTB was not detected on Xpert at the start of treatment: It is important to recheck a sputum specimen at the end of the initial phase in case of disease progression (due to non-adherence or drug resistance) or an error at the time of initial diagnosis (i.e. a true smear-positive patient was misdiagnosed as smear-negative). Those with sputum smears negative at 2 months need no further sputum monitoring. They should be monitored clinically; body weight is a useful progress indicator.

Previously treated Bacteriologically confirmed having sputum smear-positive pulmonary TB patients and/or MTB detected on Xpert and rifampicin resistance detected receiving first-line anti-TB drugs Sputum smear examination is performed at the end of the initial phase of treatment (the third month), at the end of the fifth month and at the end of treatment (the eighth month).

Table-16: Monitoring schedule for assessing treatment response

	Method	Frequency	Remarks
Treatment Compliance			
All TB patient	DOT	Daily	
Response to treatment			
Pulmonary TB Case			
New B+	Bacteriological - AFB microscopy	Month 2,5,6 (sputum microscopy)	Record results in TB treatment card /TB register
Previously treated TB		Month 2,5,6 (sputum microscopy)	
Clinically diagnosed		Month 2 (sputum microscopy)	
ALL TB patients PTB /EPTB (B+ and CD)	Clinical symptoms / Weight	Monthly (monitoring)	Record in TB treatment card Dosages should be adjusted if weight changes
Extra-Pulmonary TB	Clinical symptoms / Weight	Monthly (monitoring)	Record in TB treatment card

A positive sputum smear at the end of the initial phase at any of the other points in time may indicate any of the following:

- the initial phase of therapy was poorly supervised and patient adherence was poor;
- poor quality of anti-TB drugs;
- doses of anti-TB drugs are below the recommended range;
- resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- there are co-morbid conditions that interfere either with adherence or with response;
- the patient may have drug-resistant M. tuberculosis that is not responding to first-line treatment;
- Non-viable bacteria remain visible by microscopy (3).

With wider availability of GeneXpert, screening for Rifampicin resistance is recommended at time of registration. Xpert MTB/Rif assay is not recommended for monitoring response to treatment however patient may be referred for Xpert testing for diagnosis of rifampicin resistance if AFB smear is positive on follow-up examination in situation when

- Xpert testing was not performed before /start of treatment or
- Smear grading results is higher than zero-month smear grade
- AFB smear was negative at start of treatment

It is unnecessary, unreliable and wasteful of resources to monitor the patient by chest radiograph.

Monitoring of adverse drug effects

- All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruptions.
- A written record of all medications given, bacteriological response and adverse effects should be maintained for every patient on the TB Treatment Card (TB 02)
- Sputum should be collected from all PTB patients when the patient is given the last dose of the initial-phase treatment.
- Patient treatment records should be reviewed with the responsible health care worker, and reasons for any interruptions should be explored and addressed.
- Patient weight should be monitored each month, and dosages should be adjusted accordingly.

Identifying and managing adverse effects

Screening for adverse effects of anti-tuberculosis drugs is essential part of follow-up at the BMU (hospital). It is very important component of the TB care because adverse effects are difficult to recognize.

This is mostly done by interviewing attendant/patients and/or treatment Supporters when they visit the BMU (hospital). There are two main types of adverse effects of anti-tuberculosis drugs, major and minor adverse effects.

Major Adverse Effects: are those that give rise to serious health hazards. In this case, STOP all anti tuberculosis drugs immediately and the patient should be referred to a hospital specialist.

- The adverse effects occur in 5-10% of the patients treated for TB.
- If no response, exclude other possible reasons

Table 17: Adverse effects and their management

Adverse-affects	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	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 weekly drug intake (including rifampicin) should not be used anymore in the treatment of TB in Jordan

Table-18: Sputum smear examination schedule according to classification of TB patient

AFB sputum microscopy	Xpert	Case definition	Remarks
New B+PTB			
0 Month			
Positive	Xpert-MTB/RIF Not done	B+PTB	START treatment initial phase (2HRZE)
Positive	MTB+/ RR-Not Detected	B+PTB Rifampicin resistance not detected	
Negative	MTB+/ RR-Not Detected		
NOT done	MTB+/ RR-Not Detected		
End of 2 month			
Negative		Sputum converted	START continuation phase treatment (4HR)
Positive		Failure to convert	*Do Xpert MTB/RIF if at 1)was not done at 0M or 2) AFB sm was –ve or 3)AFB sm is higher grade positive then at 0M.
	MTB+/RR-Not detected		Start continuation phase treatment.
	MTB+/RR-Detected		Refer to PMDT site for Management of DRTB
End of 5 month			
Negative			Continue continuation phase treatment
Positive		Treatment Failure	Do Xpert MTB/RIF if 1) was not done at 0M and 2M or 2) AFBsm was negative at 0M or 2M or 3) AFB sm is higher grade positive then at 0M or 2M.
	MTB+/RR-Not detected		For further management refer protocol for treatment for previously treated
		MTB+/RR-Detected	RR-TB case
End of 6 month			
Negative		Cured	Stop treatment and declare treatment
Positive		Treatment Failure	*Follow protocol as mentioned above for “End of 5M”

9.4 Treatment Outcomes

The TB care facility will declare treatment outcome for registered TB patients on quarterly basis, based on the data recorded in TB01 card & TB03 register. The NTP has given definitions for various treatment outcomes of the TB patients. The definitions used are compatible with international suggestions. The treatment outcomes are explained in some detail in table below:

Table-19: Treatment Outcomes

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 smear positive patient who has completed the duration of treatment and have at least one follow up smear negative results but none at the end of treatment due to any reason.
	Smear negative and extra pulmonary cases complete six months of treatment successfully.
Treatment failure	A sputum smear positive patient who remains or becomes sputum smear positive at month five or later.
Died	A patient who dies for any reason during the course of TB treatment.
Lost to follow up	A patient whose treatment was interrupted for two consecutive months or more after last medicine intake.
Not evaluated	A TB patient for whom, no treatment outcome is assigned (includes "Transfer out" to another treatment unit and his/ her treatment outcome is unknown).

9.5 Follow-Up after completion of treatment

It is very unlikely and a rare event when a person successfully completes his/her full course of TB treatment and a successful treatment outcome is declared. It is therefore unnecessary to follow these patients. Patients who have successfully completed their treatment should, however, be told to report for re-examination if symptoms recur and the procedure described under "Diagnosis of Tuberculosis", should then be followed.

Chapter-10 TB Contact Investigation

Tuberculosis (TB) contacts are people who have close contact with patients with infectious TB. As they are at high risk for infection, TB contacts should be investigated systematically and actively for TB infection and disease. Such interventions are called 'tuberculosis contact investigations'. They contribute to early identification of active TB, thus decreasing its severity and reducing transmission of *Mycobacterium tuberculosis* to others, and identification of latent TB infection (LTBI), to allow preventive measures (19).

Many studies in countries with a high TB incidence have shown that the prevalence may reach 5% or more among contacts, particularly among household members. Effective investigation of TB contacts within national TB Programmes and other services can result in the detection of a significant number of cases but TB contact investigations are rarely and inconsistently carried out in resource-limited settings including Pakistan.

Other data also suggest that contact investigations could be particularly useful for identifying childhood TB. Furthermore, contact investigation can help identify people who require careful follow-up, such as those who were exposed to an index case of multi-drug-resistant or extensively drug-resistant TB or people infected with HIV, whose risk for rapid progression to active TB is very high.

Index case (index patient)

Index case is the initially identified case of new or recurrent TB of any age in a specific household or other comparable setting in which others may have been exposed.

Contact

Any person who has been exposed to an index case. Contact may be:

Household contact: A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode

Close contact: A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Contact investigation

A systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal also includes testing for LTBI to identify possible candidates for preventive treatment

Contact investigation are centered around an index case which generally is the case identified initially, but may not be the source case. Exposure of contact to index TB case may be intense or casual, easily identified or obscure. 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.

Within households, there is a gradation of exposure, ranging from sharing the same bed as the index case to living in the same compound but not in the same enclosed space. Quantification of the amount of exposure, estimated as the time spent with the index case, is likely to be highly subjective. For this reason, the infectious period for the index case is set somewhat arbitrarily at 3 months before initiation of treatment rather than relying on recall by the index case of the time symptoms began. The 3-month period is a general guideline; the actual period of infectiousness may be longer or shorter. For example, prolonged infectiousness may be associated with non-adherence (if directly observed treatment is not being used) or with unrecognized or untreated MDR-TB or XDR-TB.

Out-of-household exposure is as likely to result in transmission as household exposure e.g. in school, work place 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 culture and of behavioral patterns in order to focus contact investigations.

It is recommended that contact investigation be conducted for household members and close contacts when the index case is:

Bacteriologically confirmed pulmonary TB case diagnosed and registered at the clinic

- Suspected or proven case of drug resistant TB

- Child <5 years of age (To find source case; implies infectious case in same household)
- HIV positive (Increase likelihood of other HIV positive persons in same household with higher risk of TB if infected)
- Known or suspected of having immune-compromising conditions (such as diabetes, chronic renal failure)
- More than 60 years of age, malnourished (appears to have low body weight), smoker and have occupation that is considered high risk for TB (ceramics worker, cement factory worker, miners, painter etc.)

Contact investigation would not usually be conducted for an index case with only extra-pulmonary TB, except children < 5 years of age, in whom investigations would be undertaken in an attempt to identify the source case.

Contact identification

A systematic process to identify contacts, of all bacteriologically positive should be assessed to determine whether contact investigation should be undertaken;

Contact clinical evaluation

The goal of clinical evaluation is to diagnose or exclude TB. Clinical evaluation is undertaken if the results of contact identification and prioritization indicate a risk for having or developing TB. Clinical evaluation of household and close contacts for active TB is recommended as a priority on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to contacts

- Of all ages with symptoms suggestive of TB,
- Children < 5 years of age,
- with known or suspected immune-compromising conditions (especially PLHIV) and
- of MDR-TB or XDR-TB (proven or suspected).

Symptom screening

The patient shall be explained the importance of contact screening to bring the household members to get screened. All contacts should be asked to visit the TB Care Facility at their earliest convenient date for investigation (not later than one month) a more extensive assessment for TB disease which may include: A more detailed medical history

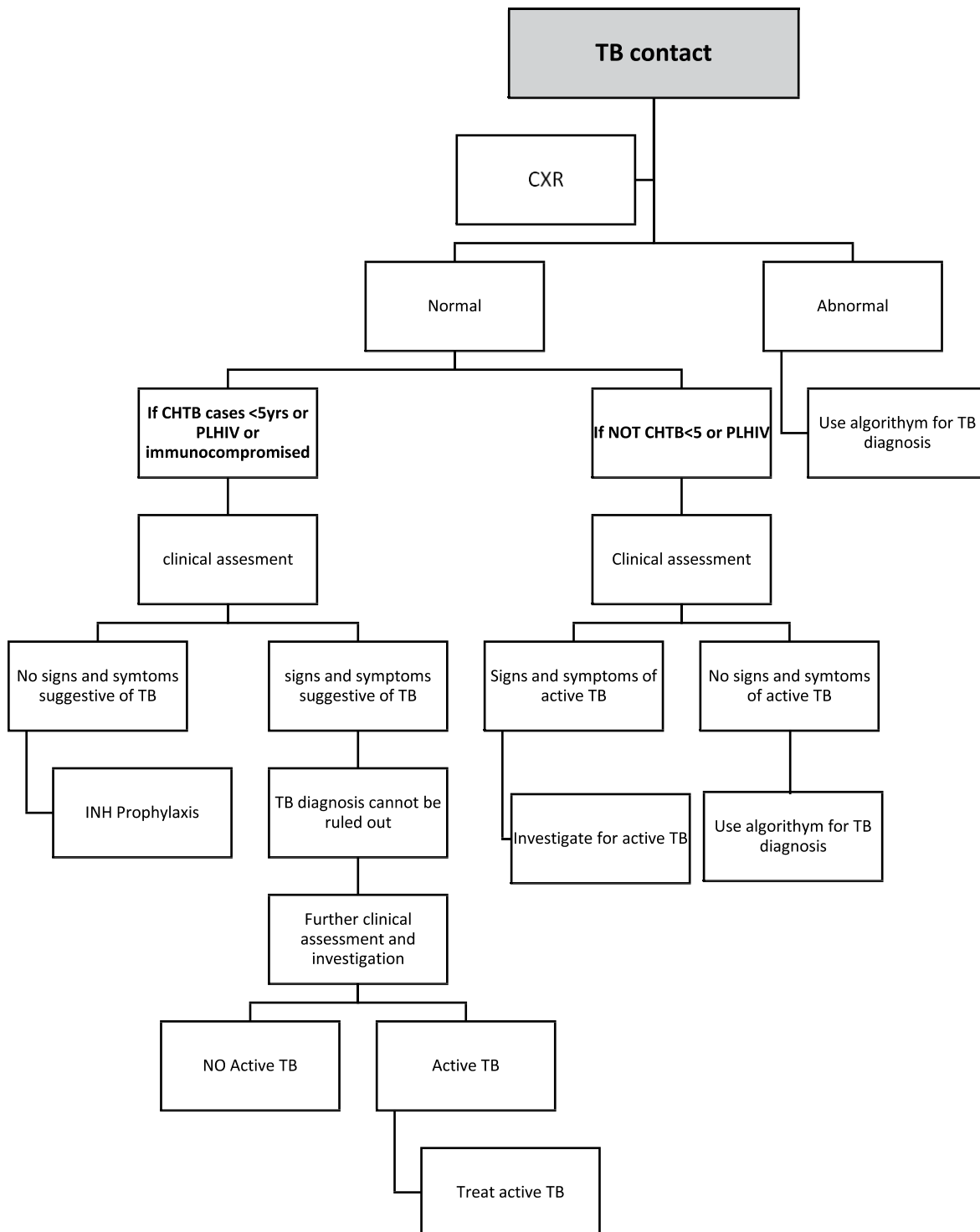
- A physical examination
- Radiographic examinations
- Microbiological assessment of specimens from sites of suspected involvement
- Invasive diagnostic tests.

Table-20: Management of Contacts

Contact	Screening	Action
Adult	Chest symptoms (Cough \geq 2 weeks with or without other TB symptoms)	Do sputum testing / other investigation , if needed
Child Under 5 years of age	No symptoms	Reassure and check for BCG scar Refer for BCG vaccination, if not already given Prescribe INH in a dosage of 10 mg/kg body weight daily for a period of six months
	With symptoms	Evaluate for TB
Child breast fed by Smear-positive mother		Treat the mother with anti-TB drugs Protect the child with INH 10 mg. /kg/day, for 6 months. Continue breast-feeding At completion of 6 months, give BCG, if not already given.

Figure 7: ALGORITHM TO SCREEN AND EVALUATE TUBERCULOSIS CONTACTS

Figure 7: ALGORITHM TO SCREEN AND EVALUATE TUBERCULOSIS CONTACTS



Chapter-11 Management of Latent TB Infection

Background

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB (21). As there is no “gold standard” test for LTBI, the global burden is not known with certainty; however, up to one third of the world’s population is estimated to be infected with *M. tuberculosis* (22) and the vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk for active TB disease and for becoming infectious. Several studies have shown that, on average, 5–10% of those infected will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection (23). The risk for active TB disease after infection depends on several factors, the most important being immunological status.

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy (24). The efficacy of currently available treatments ranges from 60% to 90%. Mass, population-wide LTBI testing and treatment are not feasible because the tests are imperfect, there are risks of serious and fatal Side-effects, and the cost would be high, for an unproven public health impact. For infected individuals in population groups in which the risk for progression to active disease significantly exceeds that of the general population, however, the benefits are greater than the harm.

Rationale

Current WHO guidelines on LTBI are based on the probability that the condition will progress to active TB disease in specific risk groups, on the underlying epidemiology and burden of TB, the availability of resources and the likelihood of a broader public health impact. Therefore, management of LTBI is recommended for people living with HIV(25)Thailand, between August 2002 and September 2003. During the study period, 342 index cases with sputum smear positive pulmonary tuberculosis patients were recruited into the study and their 500 household contacts aged under 15 years were identified. The prevalence of tuberculosis infection among household contacts was found to be 47.80% (95%CI = 43.41-52.19 and for children under 5 years who are household contacts of people with pulmonary TB(26) and for adult contacts of people with TB and other clinical risk groups living in settings with a low TB incidence (estimated annual TB incidence rate < 100 per 100 000 population)(27,28)5562 contacts of INH-susceptible and 779 contacts of INH-resistant patients and 246,845 persons with no TB case in the home were followed for 15 years, with surveys every 2.5 years comprising radiographic and sputum examination, selective follow-up of high-risk individuals and passive surveillance. If a new case developed, the household members were assigned to the ‘INH-susceptible’ (n = 7088).

Table-21: The difference between Latent TB Infection and TB disease

A Person with Latent TB Infection	A Person with TB Disease
Has no symptoms	Has symptoms that may include a cough that lasts 2 weeks or longer, coughing up blood or sputum, weakness or fatigue, weight loss, no appetite, chills, fever, sweating at night, pain in the chest
Does not feel sick	Usually feels sick
Cannot spread TB bacteria to others	May spread TB bacteria to others
Usually has a skin test or blood test result indicating TB infection	Usually has a skin test or blood test result indicating TB infection
Has a normal chest x-ray and a negative sputum smear	May have an abnormal chest x-ray, or positive sputum smear or culture
Needs treatment for latent TB infection to prevent TB disease	Needs treatment for TB disease

Eligibility for Programmatic management of LTBI

Not all individuals infected with *M. tuberculosis* develop active TB. It is estimated that the lifetime risk of an individual with LTBI for progression to active TB is 5–10% (23). The risk is particularly high among children under the age of 5 years and among people with compromised immunity (21). As preventive treatment entails risks and costs, preventive treatment of *M. tuberculosis* infection should be selectively targeted to the population groups at highest risk for progression to active TB disease, who would benefit most from treatment of LTBI.

Management of LTBI involves a comprehensive package of interventions: identifying and testing those individuals who should be tested, delivering effective, safe treatment in such a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation of the process.

Preventive treatment is recommended for:

- All contacts of bacteriologically confirmed pulmonary TB case
- PLHIV and
- Well specified other high-risk groups which include, in the context of Pakistan:
 - 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;

Note: LTBI 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.

Who does not require a diagnosis of LTBI before initiation of preventive treatment?

The TB contacts, PLHIVs, and high risk groups like patients initiating anti-TNF treatment, receiving dialysis, preparing for an organ or hematological transplant, patients with silicosis **do not** require a diagnosis of LTBI for initiation of preventive treatment however these groups must be evaluated to exclude active TB disease before the initiation of preventive treatment.

Adults, adolescents, children and infants living with HIV

- Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and are unlikely to have TB disease should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women.
- Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease.
- Children aged more than 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening
- for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB.
- All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months.

Other HIV-negative at-risk groups

The systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants, homeless people and people who use illicit drugs.

Systematic testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations.

11.1 Diagnosing Latent TB Infection & Disease

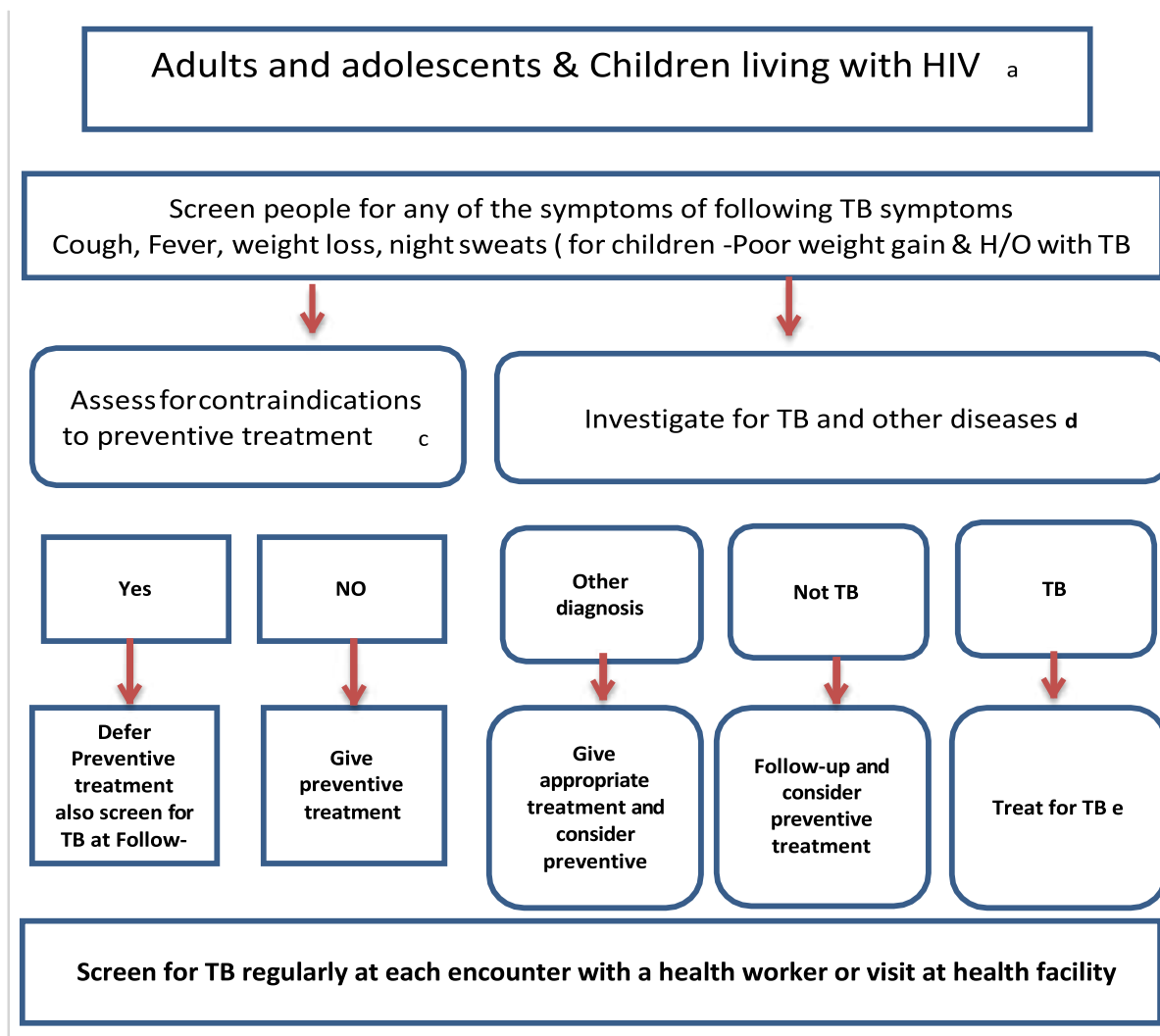
Most persons, but not everyone, with TB disease have one or more symptoms of TB disease. All persons with either symptoms or a positive TB test result should be evaluated for TB disease. If a person has symptoms, but a negative TB test result, they should still be evaluated for TB disease.

A. Diagnosis of Latent TB Infection

A diagnosis of latent TB infection is made if a person has a positive TB test result and a medical evaluation does not indicate TB disease. The decision about treatment for latent TB infection will be based on a person's chances of developing TB disease by considering their risk factors.

1. **Medical History.** Clinicians should ask about the patient's history of TB exposure, infection, or disease. It is also important to consider demographic factors age, ethnic or racial group, occupation that may increase the patient's risk for exposure to TB or to drug-resistant TB. Also, clinicians should determine whether the patient has medical conditions, such as HIV infection or diabetes that increase the risk of latent TB infection progressing to TB disease.
 2. **Physical Examination.** A physical exam can provide valuable information about the patient's overall condition and other factors that may affect how TB is treated, such as HIV infection or other illnesses.
 3. **Test for TB Infection.** The Mantoux tuberculin skin test (TST) or the IGRA may be used to test for *M. tuberculosis* infection. Additional tests are required to confirm /exclude TB disease.
 4. **Chest Radiograph.** A posterior-anterior chest radiograph is used to detect chest abnormalities. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. However, a chest radiograph may be used to rule out the possibility of pulmonary TB in a person who has had a positive reaction to a TST or TB blood test and no symptoms of disease.
- Deciding When to Treat Latent TB Infection

People with latent TB infection do not have symptoms, and they cannot spread TB bacteria to others. However, if latent TB bacteria become active in the body and multiply, the person will go from having latent TB infection to being sick with TB disease. For this reason, people with latent TB infection should be treated to prevent them from developing TB disease. Treatment of latent TB infection should start after excluding the possibility of TB disease.



B: Figure 8- Algorithm for TB screening for adults and adolescents & children living with HIV

- a. Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce M. tuberculosis transmission in all settings in which care is provided.
- b. Chest radiography can be done if available, particularly for people living with HIV on ART, but is not required to classify patients into TB and non-TB groups. In settings with a high HIV prevalence and a high TB prevalence among people living with HIV (e.g. > 10%), strong consideration should be given to adding other, sensitive investigations.
- c. Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. History of TB and current pregnancy should not be contraindications for starting preventive treatment. Although LTBI testing is not a requirement for initiating preventive treatment, it may be done as a part of eligibility screening where feasible.
- d. Xpert MTB/RIF should be used as the initial diagnostic test for TB. Detailed algorithms for people living with HIV suspected of having TB are available in the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf).
- e. Resume regular screening for TB after completion of treatment for active disease.

C. Testing for LTBI

- Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) may be used to test for LTBI. People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals.
- LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years.

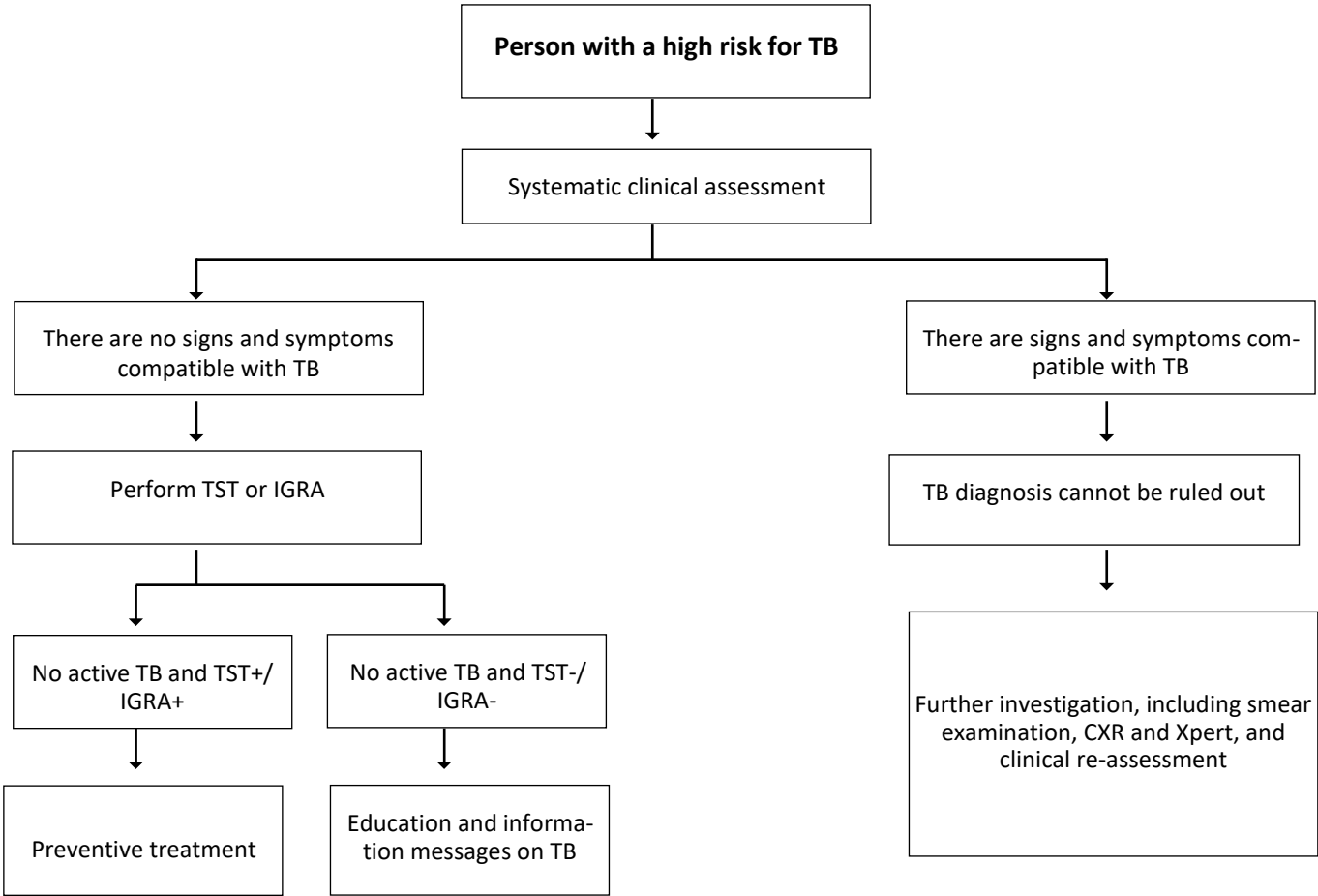
D. Treatment options for LTBI

- Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children
- Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years
- Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children more than 2 years
- The adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.

E. Preventive treatment for contacts of patients with multidrug-resistant-TB

In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.

Figure 9: Algorithm: Identification and treatment of LTBI in high-risk groups for tuberculosis



Chapter-12 Drug Resistant Tuberculosis

Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in drug-susceptible TB patients. This improper use is a result of number of actions including, administration of improper treatment, failure to ensure that patients complete the whole course. Essentially, drug resistance arises in areas with weak TB Programs. A patient who develops active disease with resistant TB strain can transmit this form of TB to other individual.

12.1 Types of Drug Resistant Tuberculosis

- **Mono-resistance TB:** resistance to one first-line anti-TB drug only.
- **Poly-resistance TB:** resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin together.
- **Multi-drug-resistance TB (MDR-TB):** resistance to at least both isoniazid and rifampicin.
- **Rifampicin-Resistant TB (RR-TB):** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, poly-drug resistance or extensive drug resistance.
- **Extensive drug-resistance TB (XDR-TB):** Resistance to any Fluoroquinolone (FQ) and at least one of the injectable second-line drugs SLIs (Amikacin or Streptomycin) in addition to multidrug resistance.

12.2 Drugs used in treatment of drug resistant TB

WHO has recently revised treatment guideline and second line drugs are regrouped as follows (29):

Group-A	Levofloxacin OR Moxifloxacin, Bedaquiline and Linezolid.
Group-B	Clofazimine, Cycloserine OR Terizidone
Group-C	Ethambutol, Delamanid, Pyrazinamide, Imipenem-cilastatin, Meropenem, Amikacin (Streptomycin), Ethionamide/Prothionamide, <i>p</i> -aminosalicylic acid

New drugs in MDR TB treatment

- Bedaquiline & Delamanid are new drugs recently introduced. Bedaquiline has strong bactericidal and sterilizing activity against *M. tuberculosis* organisms and is now recommended as core drugs in longer treatment regimen.
- Medicines no longer recommended are Kanamycin and Capreomycin, because of increased risk of treatment failure and relapse associated with their use in longer MDR-TB regimens.

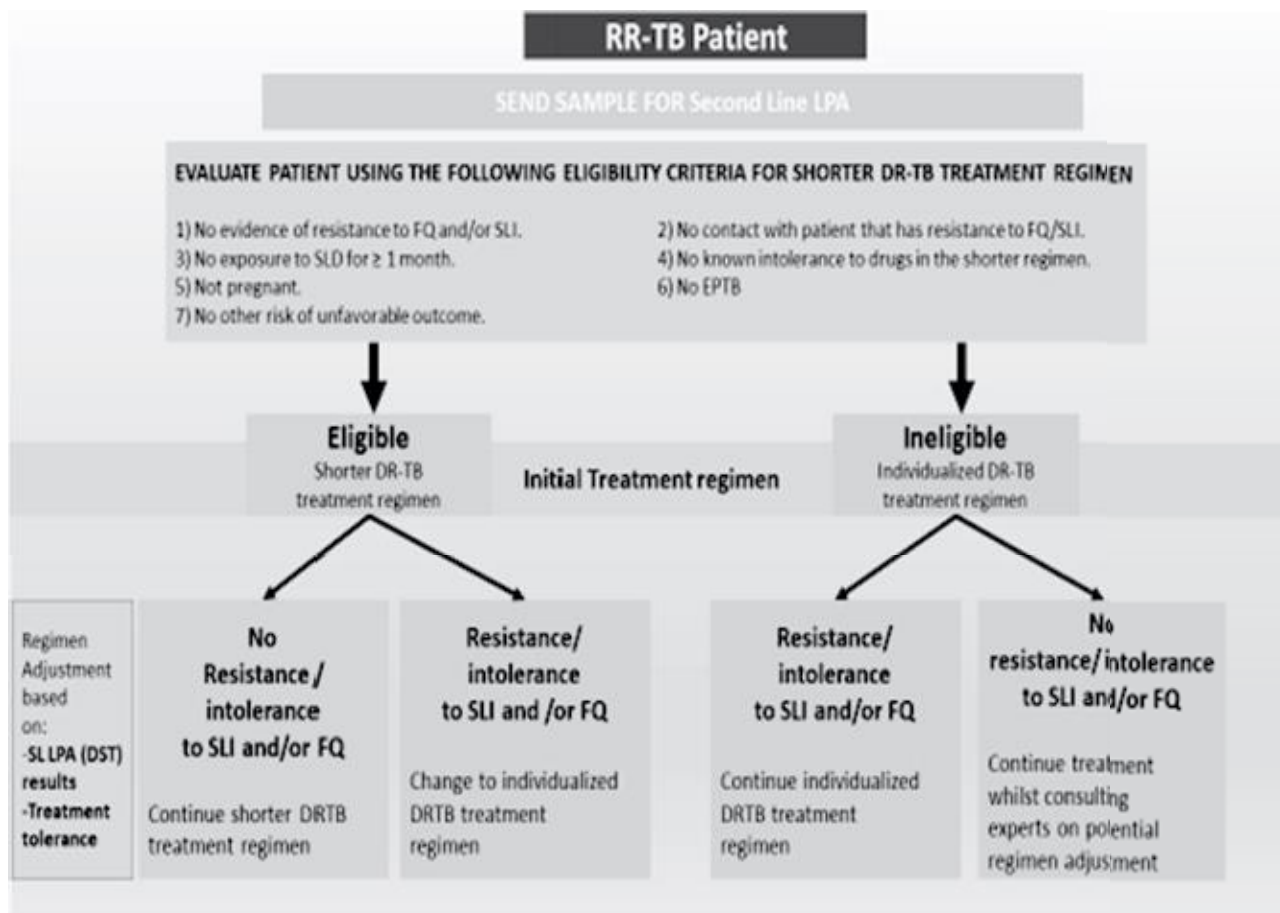
DR-TB treatment regimens

Two treatment regimens are recommended subject to drug resistance profile of Individual patients.

Longer MDR-TB Treatment regimen: Treatment duration is 20-24 months.

Short Treatment regimen (STR): In 2015 WHO released recommendation on the programmatic use of the short-course regimen for MDR TB cases (9-11 months' duration). STR is recommended for DRTB patients whose strains are susceptible to second line drugs including Fluoroquinolone and second line injectable (SLI).

Following criteria is used as guiding principles in treatment selection.



For further details on different treatment regimens refer to relevant Chapter of National Guidelines for the programmatic management of drug-resistant tuberculosis (PMDT).

12.3 DRTB disease burden and treatment services in Pakistan

Pakistan ranks 4th among 30 high Drug Resistant (DR) TB burden countries in the world with estimated 27,000 cases DR-TB cases in 2017. It is estimated that there were 15,000 MDR/RR TB cases among pulmonary TB cases notified in 2017, based on 4.2% RR/MDR in new TB cases and 16% among previously treated cases (6).

Currently, there are 33 DR-TB Treatment Sites (public and private sectors) across the country where DR-TB patients are being managed under Programmatic Management of Drug Resistant TB (PMDT). Provision of free of cost services are ensured at these designated Treatment Sites where team of trained health professionals manage DRTB patients in collaboration with technical assistance from central level. Package of comprehensive care is provided which include proper diagnosis, precise treatment prescription by trained medical providers and comprehensive psycho-social support care. The DR-TB patients are managed as per DR-TB protocols laid down in National Guidelines to avoid risks related with misdiagnosis, use of inappropriate treatment, use of suboptimal quality drugs and improper management of adverse events related with these drugs. It is suggested that the treatment may be confined to designated PMDT Treatment Sites for provision of best possible care to patients.

Ambulatory based-model of Care

Majority of the DR-TB patients are managed through ambulatory care model of treatment. After careful clinical assessment, treatment supporters are identified and information is provided of nearby public sector TB care facility. All DR-TB patients visit PMDT Treatment Sites on monthly basis for follow-up assessments, including clinical monitoring, drug compliance and sputum cultures for monitoring of treatment response.

Hospital-based model of Care

All PMDT site are equipped with facilities of indoor management. Although hospitalization is not prerequisite for initiating DR-TB treatment, but some of the newly diagnosed DR-TB patients may require hospitalization (at PMDT Treatment Site) to make clinical assessment, observe poor clinical condition and initial response to the prescribed second line drugs (SLDs) and to make satisfactory arrangements for ambulatory-based management of DR-TB patient.

Social Support Package

The compliance to DR-TB treatment is a significant challenge for the patient & care givers/families due to length of treatment and adverse events related with DR-TB drugs. In addition, long distance travels are required to access quality care resulting high out of pocket expenditure. Keeping in view these barriers and constraints to successful treatment, social support package is provided to DR-TB patient and the treatment supporter. This enables the patient to improve their nutritional status and cover the travel expenses. The mobile cash-based disbursement mechanism through Easy Paisa is implemented to ensure timely and transparent distribution of cash incentives.

Management of Contacts of DR-TB Patients

All close contacts of DR-TB cases are at high risk of DR-TB due to transmission of drug resistant strains from index case. Risk increase with delay in the diagnosis and smear positivity of the index case. It is therefore very important that all contact should be identified and screened for TB/ Drug resistance TB soon after the diagnosis/enrolment of DRTB patient. If any contact is reported symptomatic or has abnormal shadows on CXR, they should be immediately investigated using Xpert/ MTB/RIF testing. If rifampicin resistance is detected, then the patient should be referred immediately to the nearest PMDT Treatment site for enrolment and effective treatment.

Chapter-13 Tuberculosis 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.

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

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 (1).

13.1 Principles of TB-infection Control in a Health Care Facility (2)

A: Managerial Control

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

- Identification of a coordinating (IC) body and development of 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.
- Site risk assessment to ensure appropriate use of available spaces to optimize the implementation of infection control measures
- Surveillance of TB disease for health care workers
- Advocacy, communication and social mobilization including engagement of civil society
- Monitoring and evaluation of TB IC measures
- Operational research

B: 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
- 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 piece of cloth; tissue papers or surgical masks may also help spread of transmission.
- Reduction of diagnostic delays
- Prompt initiation of treatment

C: 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. 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. However, due to the expensive maintenance it may be feasible in a high resource setting.

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.

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. Strong behavioral change campaigns are to be preceded to avoid stigma associated with its use.

In addition to complying with cough etiquette patients may also make use of surgical mask especially while visiting a health facility. This helps in reducing disease transmission mainly by reducing 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)
- At areas with high generation of aerosols bronchoscopy, intubation, sputum induction procedures, aspiration of respiratory secretions, and autopsy.

13.2 Pathway of a patient and infection control measures in a 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
Prolonged waiting	Fast track TB suspects and cases to the front of the line to expedite their receipt of services
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: <ul style="list-style-type: none"> • 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.
Interaction with HCW during check up	In a low resource setting, HCW may interact with the patient in a well ventilated open area. 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.

Sputum collection	Collection of sputum collection in a well ventilated 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.

13.3 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.

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.

Any health care provider while visiting a smear 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 health center to establish 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 prophylaxis therapy IPT (3).

TB Control in Pakistan: Approaches and implementation Strategies

Chapter-14 Engaging all health care providers in TB control

In Pakistan, there are evidences that private sector is the first point of contact in >80% of the patients with various type of ailments and many patients with symptoms of TB, including the very poor, do seek and receive care from a wide variety of health care providers outside the network of NTP services. These include private providers (for profit and not-for profit e.g. GPs, private hospitals and NGOs) and other public sector institutions such as Army, Railway, Social Security, etc. Many of these health care services are not notifying TB cases to NTP and quality of TB services and treatment outcome in this sector is mostly unknown

DOTS implementation in the public sector is almost fully covered but only a small fraction of private sector is engaged/ reporting to NTP. Engaging all health care providers in TB control was an essential component of WHO Stop TB strategy, and is a major component of new END TB Strategy & Pakistan National TB Strategic Plan 2017-2020.

The NTP/PTP is in the process of consolidation and scaling up DOTS activities through several innovative approaches by engaging all care providers

Guiding Principles for Public Private Mix approaches in TB control

Following principles are recommended for public private partnership:

- The National policy for Mandatory TB case Notification is applicable to all health care (Public& Private) providers.
- Recommended Diagnostic & treatment protocols shall be adopted by Private providers
- TB Programme 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 patient 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,
- The 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 use. 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 stake holders.
- Standardized training protocols is recommended however specific training modules and methodology may be contextualized based on private sector demand and limitation.

The Public – Private –Partnership Models in Pakistan

There are four basic models under the Public-Private Partnership (PPP). In all these models technical support including training, drugs and diagnostics, recording and reporting tools is provided by Provincial TB control Programme through the district TB program. TB cases are notified to the district notification system.

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, provision of logistics and organizing community awareness activities.

In this model different “network of non-government organizations providing health care” are engaged.

In this model private hospitals including large tertiary Care Hospitals e.g. (Gulab Devi, AKU and Indus Hospital) are engaged. The Other public sector model includes those public sector organizations which are not under 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.

Mandatory TB case notification:

TB is a notifiable disease in Pakistan and all health care providers are bound to report the diagnosis, prescription and sale of anti TB drug with a week to the district health authorities. The pilot project is initiated in Sindh and KP provinces.

Chapter-15 Hospital DOTS 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.

Large number of TB patients are feared to be missed as presumptive TB cases are scattered across large hospital and effective linkages are lacking between different departments and there is no centralized reporting systems for TB cases e.g. SOP for reporting TB patient diagnosed in orthopedic OPD /ward or in cancer ward are not developed nor implemented and therefore even though hospital has TB care services mostly run by pulmonology and pediatric department, but not all TB patients diagnosed are reported. Furthermore, patients coming to these hospitals from distant places are also more vulnerable to loss to follow up if not properly referred back to facilities close to their residence for treatment.

Objective and key Recommendation

The HDL seeks to bring the national guidelines on TB case management to ensure access to quality DOTS services for TB patients seeking care from these hospitals. Following is recommended in this regard:

(1) Build an Internal Network

Objective of the internal network is to capture all TB patients seeking care from large hospitals that would otherwise be "missed. The network ensures standardized TB care for all patients presenting to any of the different departments within the hospital and thus will improve TB case notification and treatment compliance by reducing missing /loss to follow up cases Internal network: ". Following intervention are recommended for an effective network.

- Sensitizing key facility staff (ward/OPD etc.) on
 - Identifying presumptive TB cases e.g. Coughing patient in Obstetric OPD or Orthopedic OPD need to be investigated for TB same as coughing patient presenting in chest OPD.
 - Reporting of diagnosed TB case e.g. EPTB case diagnosed clinically /histopathology/X-Ray (e.g. with TB spine in orthopedic ward or TB abdomen in general medicine ward) or PTB diagnosed based on investigation conducted in private laboratories.
 - Use of standardized reporting and recording tools and central reporting of TB case diagnosed
- Defining the mechanism by which such patients shall be referred to the DOTS center nearest to their residence
- The doctors & nurses shall be sensitized on available TB diagnostic services and anti-TB drugs as well as on NTP guidelines on TB diagnoses and treatment

For NTP recommended Framework of Action for HDL: See Annex-1

Enhanced case finding: All patients & their attendants attending various OPDs in hospital may be screened using mobile van (fitted with CAD digital X ray & Xpert) approach to identify TB presumptive (score >70) for further investigation. Build an External Network

Objective of this network is to reduce loss to follow up by referring patients coming from distant places to appropriate TB care facilities close to their residence.

An effective "**external network**" will ensure that enrolled patients successfully complete their treatment. An updated directory of the Health care facilities offering TB DOTS services within each district /province shall be available with HDL coordinator. Importance of treatment compliance shall be discussed with the patient and referral shall be offered to patient coming from distance according to their home address or any other preferences. Patient shall be referred with a referral form and 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 Dots 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.

Monitoring and supervision

An HDL intervention shall be monitored for effectiveness of:

Internal network: The referral trend / TB cases notified by department other than the one hosting DOTs clinic

External Network: The referral trend (i.e. referral and uptake) of diagnosed Tb cases to other Health care facilities for registration/ treatments.

Chapter-16 TB care in Prisons & other 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.

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 prisoners² 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 recommendation to implement TB care in congregate settings

A Systematic approach is recommended to introduce a TB Control Programme 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 Programmes
- Advise /Implement Infection control measures based on baseline assessment.

TB care services in Prison

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 DOTS services shall be established for diagnoses and treatment of patients on routinely basis. DOTS services ensure:

- Diagnosis of a TB cases through entry screening as he enters prison and
- 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.

Detect TB through Active Case Finding and Symptom Screening

- 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 screened 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 specimen.

Mass Screening in prison populations

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

Contact Investigation

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

Chapter-17 TB care and control in Refugees and Displaced population

Background

The Office of the United Nations High Commissioner for Refugees (UNHCR) has estimated that there are around 2.4 million registered Afghan refugees are living in the Islamic Republic of Pakistan (Pakistan) of which 1.4 million refugees hold Proof of Registration cards. More than 1 million and over 610,000 documented and undocumented Afghans refugees returned from Iran and Pakistan to Afghanistan in 2016 and 2017 respectively.

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. The burden of tuberculosis (TB) in Afghan returnee populations (refugees and undocumented persons) is reported to be three times higher than in the general Afghan population.

Afghanistan, Iran and Pakistan have established strong national tuberculosis (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 strengthening collaboration between countries to provide quality TB care to the target population

1. Establish inter-county coordination mechanism/steering committee.
2. The TB service provision shall be harmonized among the three countries.
3. The segregated information on migrants, refugees, returnees and IDPs with TB should also be collected routinely and recorded within the NTP networks.
4. Development of a multi-country TB database that will allow cross-country tracking of patients and evaluation of treatment outcomes.
5. The country protocol shall be available in all treatment facilities engaged in cross border TB management.
6. The recording and reporting as well as the monitoring and evaluation system shall also be incorporated.
7. Strengthening of diagnostic services in refugee settings with provision of active case finding activities in refugee settings.
8. Use of innovative technologies for treatment support and referrals.
9. Targeted information and education activities in refugee, migrants and returnees' settings.
10. Address removing human rights and gender related barriers to TB care and prevention.
11. Prepare contingency plans in advance for episodes of insecurity, unexpected movement of the camp or population, and repatriation or transfers to another Programme.
12. 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-18 Monitoring and Evaluation

Monitoring and evaluation is considered to be the backbone of a public health programs. A well-established M&E function is part of program. Primary objective of this function is to monitor various interventions implemented by the program and to collect the validated data quarterly through a series of quarterly meetings. The data thus collected is disseminated by NTP data to national and international stakeholders.

Monitoring and evaluating in TB control implies assessing program activities on regular basis i.e. quarterly and yearly, determining the extent of programme coverage, evaluating the case notifications & treatment outcomes trends, and determining the impact of the programme on the epidemiology of the TB disease.

M&E tells us:

- Where we are now.
- Where we are likely to go in future.
- Extent to which programme goals & objectives are being achieved or likely to be achieved.
- How program performance can be improved
- Whether the program is worth implementing

The monitoring visits in TB control should ensure that work is being carried out along the NTP guidelines/SOPs, so that at the end of the reporting period, data is timely collected, analyzed.

Following are some of the characteristics of good monitoring activities in TB control:

1. Monitoring involves the selection of TB control indicators that reflect the permissible range of performance.
2. It involves the gathering of information on how implementation is actually performed and comparing it against the desired standards.
3. If needed taking corrective actions if deviations occur, provide timely feedback.
4. Manage data efficiently and effectively, which is a key to the Quality Assurance Program.

18.1 M&E System

Provincial and national M&E units comprise of various monitors especially recruited for monitoring of activities with local and donor support. In addition to these monitors specific intervention coordinators are also there who are not only responsible for implementation of specific intervention but also support the program in regular monitoring and supervision of programmatic and diagnostic activities. M&E unit at national level in addition to the responsibilities explained above at provincial level also responsible for policy guidance and technical support of the units at provincial/ regional level.

Monitoring and supervision is carried out in accordance with national and provincial monthly plans with help of a structured checklists comprehending the entire dimensions of the program and various interventions.

18.2 M&E tools

Program as a policy is implementing structured M&E to ensure monitoring of all essential components in a visit. A uniform mechanism is recommended for planning and approvals of the visits. Visits are carried out with the help of a structured checklist.

M&E indicators: M&E indicators are subdivided in;

- **Input indicators:** these indicators consist of a set of indicators referring to various logistic and programmatic inputs like reagents, medicine, health Education material, trainings of various cadres, guidelines and manuals.
- **Process indicators:** the indicators pertaining to processes like presumptive identification, referral to lab & Xpert and BSL labs, sputum transportation mechanisms, various measures of active case finding etc. and intervention specific indicators are included in this group.
- **Output indicators:** TB data is collected and analyzed on quarterly basis and output indicators include case detection of DS, DR and pediatric TB and treatment success rate of various type of cases. Intervention specific output indicators are also included in this group.
- **Impact indicators:** this refers to incidence and prevalence of different types of tuberculosis and to mortality related to TB and are not calculated in routine. The data collected by routine recording and reporting system is analyzed by epidemiologists (usually at WHO level) to measure these indicators.
- **Donor specific indicators:** NTP strives hard to implement various interventions recommended in National Strategic Plans to control TB in the country. In case of deficient funding, the donors are approached for support. Some intervention, specific indicators/ tracking measures are also included in the checklist/ scope of monitoring as and when required.

Data recording tools

TB data recording system start from the facility outdoor register. Presumptive of Tuberculosis are identified among the patients visiting OPD. They are referred to laboratory for sputum smear microscopy (**TB 05**) or Xpert analysis. Complete personal information and results are recorded in **TB04 register**. Results are provided back to medical Officer who decides about the diagnosis of patient. The diagnosed case is referred to TB DOTS section after making relevant entries in OPD register.

In DOTS section patient is received by DOTS facilitator who prepare patient file by completing **TB01 (Pt. facility card) & TB02 (Pt. Card indicating follow up visit dates)**. The information is translated to **TB03 (facility TB register)**.

Data reporting tools

TB data is reported on quarterly basis. Two types of reports are generated one on cases detected in previous quarter i.e. **TB07** and treatment outcome of patients registered in corresponding quarter of last year (**TB 09**).

Data validation

Data is reported to provincial level after validation. The validation process is carried out at district level by the district TB control Officer with the technical support of provincial Program Officer or a technical officer from provincial level.

Quarterly surveillance and review meetings

A series of quarterly surveillance and review meetings are scheduled by the program to carry out validation of the data at district level and to review the quarterly progress at district, provincial and federal level. The objectives, process and outcome of these meetings are narrated below.

- **Intra-district meetings:** Primarily these meetings are designed for data validation. All the medical officers, para-medics (DOTS facilitator) and lab technician of BMU in the district come to district headquarter level for one-day meeting. They bring the recording instruments i.e. TB01, TB03 & 04 and two reports i.e. TB07 & TB09. The reports are validated by DTC with technical support of PPO/ expert from province. The meetings are chaired by DHO/ EDO of the district who is appraised of achievements and short comings. He is supposed to support the BMUs in administrative problems.
- **Inter-district meetings:** this meeting is convened at provincial headquarter on quarterly basis after completion of intra-district meeting in all the districts. PTO present the aggregated data of the province and individual data of each district. Updates and trend analysis is shared. This meeting is primarily aimed to review the performance of the districts in preceding quarters.
- **Inter-Provincial meeting:** This meeting is convened at federal level after the completion of inter-district meetings in all the provinces. Aggregated national data is shared with PTPs and partners. Trend analysis is done and group work is done to address the programmatic shortcomings.

DHIS-2 system, introduction and progress

DHIS2 system for data entry and analysis is being introduced in the country with technical support of university of Oslo. Districts are being provided with laptops and end users are being trained. The system will replace the excel system and real time data may be entered and viewed. To start with aggregate data is being entered and latter case based data entry (tracker system) will be adopted.

Cohort analysis in TB control

A cohort is a group of patients diagnosed and registered for treatment during a specific time period (a quarter of the year). Cohort analysis is the key management tool for evaluating the NTP/PTPs performance. It allows the identification of technical problems, so that the NTP/PTPs can institute appropriate action to overcome them and improve programme performance.

TB data analysis and use must be done at health care facility, district, provincial and national levels. It is the duty of the focal points at respective tiers to validate, analyse the data and submit it timely to the next level. The recent developments for END TB strategy implementation demands such analysis and NTP has a plan to implement DHIS 2 on aggregate module which will facilitate such robust meaningful analysis.

Defining a multi-sectoral approach

“A multi-sectoral response means involving all sectors of society - governments, business, civil society organizations, communities and people living with TB, at all levels - Global, national and community - in addressing the causes and impact of the TB epidemic. Such a response requires action to stimulate political will, leadership and coordination, to develop and sustain new partnerships and ways of working, and to strengthen the capacity of all sectors to make an effective contribution.”

Why Multi-sectoral approach

- TB is not just a health issue since it affects every aspect of life and society;
- Poor health, poverty, malnutrition are important determinants of vulnerability and susceptibility to TB;
- Gender inequity demands a ‘gender lens’ be applied to all aspects of the multi-sectoral approach;
- Other cultural, social and economic factors shape the face of the local epidemic.

Key Elements of Multi-sectoral approach

- Multi sectoral approach helps in pooling the resources and formulating the common objectives.
- Willingness at the leadership and mandate at the policy level are necessary to plan and execute the successful multi-sectoral coordination.
- All the major stakeholders require to share the common vision and perspective.
- Developing institutional mechanism is utmost requirement, as it will standardize the processes.
- Promotion of multi-sectoral coordination within the health system and with other ministries is seen as an important measure for TB control in Pakistan.
- The multi-sectoral approach is proposed to build synergies across health & non-health sectors through leverage at their capacities to End TB in Pakistan by 2030.

Examples

- Ministries of Education have lead responsibility for implementing programs for teachers, schoolchildren and their parents;
- Ministries with responsibility for Gender/Women’s Affairs have a responsibility to ensure that a ‘gender lens’ is applied to all plans and programs;
- Ministries of Agriculture for agricultural extension workers;
- Ministries of Defense for the military;
- Ministries of Labour can mandate workplace prevention programs; private firms can contribute in cash and in kind.
- NGOs that are trusted by vulnerable populations are best placed to spearhead and deliver prevention and care programs, in collaboration within communities.
- The mass media can promote the basic preventive measures for TB control healthy and actively foster positive attitudes towards those affected by TB & and create demand for TB care and inform the availability of TB facilities.

Strategies for Multi-sectoral approach

The following strategies should be adopted

- a) The formation of National inter-ministerial commissions on TB, or their equivalent, by Ministries of Health in partnership with civil society.

- b) Develop mechanisms for strengthening advocacy at all levels within all relevant sectors
- c) Develop a well-defined accountability framework for monitoring and evaluation & include appropriate indicators to review processes to monitor progress toward clear goals.
- d) Engage civil society & other key stakeholders in all stages of planning cycle.

The multi-sectoral response, therefore, must:

- Be dynamic, flexible, strategic and coordinated;
- Take account of the size of the problem, identifying the vulnerable, high-risk groups;
- Involve national leaders, all government ministries and departments, with each taking responsibility for pre-determined aspects of the overall response and making the best use of its resources;
- Include sectors outside government business, civil society organizations, communities, TB associations, and others affected by the epidemic, with full recognition being given during the development of the response to existing activities, which should be built upon. Particular attention should be given to supporting existing community coping strategies;
- Define roles and responsibilities, based on the comparative advantage of each player/stakeholder. It is not always necessary or appropriate for every sector to be involved in every area of activity;
- Occur at all levels in the country and be linked to action at the international level.

The Multi-Sectoral Accountability Framework

The accountability framework should clearly explain the roles and responsibility of each sector, and include the indicators to measure progress. To maximize impact, a multi-sectoral accountability framework should be based on approaches protecting and promoting equity, gender equality, human rights and ethics.

The multi-sectoral accountability framework should enable the review and monitoring of implementation and provide a systematic approach to determine additional actions required to achieve the SDG and End TB Strategy milestones and targets.

Chapter-20 Pharmaceutical and Health Product Management

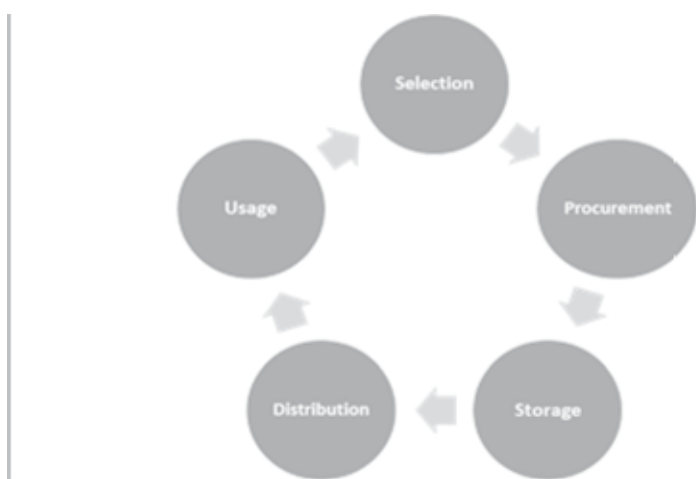
Introduction

The Pharmaceuticals and Health Products are an essential component of TB care & prevention. ATT are included in the National Essential Medicines List (NEML) and provincial MSDs/EHSP of Pakistan as well as World Health Organization EML. It should be ensured that all TB patients get uninterrupted access to recommend quality assured anti-TB treatment (ATT) medicines and laboratory supplies and should be used rationally. The diagnostic and treatment details have been described in the relevant section.

Drug Management Cycle

The TB Drug management system involves five basic functions: selection, procurement, storage, distribution, and use.

Figure-10: Drug Management Cycle



(1) Selection of product

Selection is the process of choosing the most appropriate PHPs for TB Program from a limited list of essential medicines and WHO TB Tools for labs. The selection criteria are based on WHO recommendation and national guideline and keeping in view factors such as disease prevalence, availability, costs, quality, efficacy, safety, listing in essential medicine list/formulary and simplicity of stock management and adherence to treatment by patients to the treatment protocol.

(2) Procurement of product

Procurement is the process of obtaining PHPs through a competitive, transparent and accountable process of purchase. Careful procurement planning is required at all levels for optimal use of available resources in procuring good-quality products at the most economical prices. Key consideration before procurement are:

Registration: As mentioned earlier, any PHP to be procured for use in Pakistan has to be registered with the DRAP by the potential suppliers for in country procurement. However, a waiver in registration need to be sought in case of donations (in kind) from quality assured sources abroad.

- **Quantification:** For quantification of ATT medicine, the morbidity / consumption-based method is followed. This method forecasts the future needs based on the number of expected TB and symptomatic respiratory cases, consumptions trends, available stock and stock in pipeline. The quantities of medicines to be procured are to be calculated according to 'known needs' plus a buffer / reserve stock to cover unexpected demand or delays in supply. NTP recommends 100% buffer stock to be available in country for its annual needs. The distribution of buffer stock will be as; 50% national level, 25% provincial and 25% at district level. NTP uses Quant TB software for quantification of ATT medicines. While for the procurement of laboratory supplies national TB morbidity based

forecasting method is followed.

- **Quality Assurance:** PHPs which meet the quality standards for manufacturers whose products and manufacturing sites are prequalified by the UN prequalification Program for international procurements and should be tested for BA/BE for local procurements. National TB Control Program procures pharmaceuticals and health products from international market (donor funds) as well as from local market through government funds.
 - **International procurement:** WHO recommends that national TB Program select ATT medicines & laboratory supplies from the WHO Model List of Essential Medicines & WHO TB Tool (all of them are listed by generic name or international nonproprietary name). Such selection ensures that only PHPs with scientific evidence for efficacy and safety are listed. Additionally, the selection criteria are extended to the PHPs of manufacturers listed under the WHO Certification Scheme. (WHO Prequalified Manufacturers).
 - **National procurement:** Selection of all essential medicines and laboratory supplies to be procured is authorized by the Departmental Purchase Committee, which prepares the list of products to be purchased based on (National Guidelines, EML & Lab items details) and the Rate Contract List. For quality assurance of Pharmaceutical Products, it is mandatory that only those manufacturers and products are eligible to participate in bidding who have successfully undergone the process of Bioavailability / Bioequivalence (BA/BE) studies, from WHO Pre-qualified BA/BE labs across the globe or labs those are authorized by Drug Regulatory Authority of Pakistan to conduct BA/BE studies. All government hospitals and district health departments shall adopt same criteria while procuring the ATT medicine.

(3) Storage

Good practice in the management of these storage facilities should ensure that the following protocols are fully addressed:

- Infrastructure—handling equipment, racking, shelving, movement of items, refrigeration units, powersupply, pallets
- Facility layout—zoning, materials flow, appropriate working environment
- Receipt & Issuance-----Quarantine area, Physical Inspection/Count & Inventory Control
- Electronic Recording & Reporting System-- TB DMIS and WMS across the supply chain
- Environmental conditions—room temperature (30 Celsius by max.), moisture control, dust control, control on direct sunlight, pest control
- Human resources—personnel, training, job descriptions, communications
- Security—recording systems, controlled access, building integrity, auditing procedures
- Support systems—electronic, manual, mixed, forms, instructions, reporting
- Good working practice— FEFO & FIFO stock rotation, disposals, documented procedures
- The system of Quality Assurance across the supply chain

Details on the specific requirements and instructions on Good Warehousing Practices as it relates to the TB Program can be viewed in the Operational Manuals.

Currently, medicines are mainly stored at National, provincial and district warehouses. At all these levels the Program has well established warehousing facilities which meet the requirements of Good warehousing practices (GWP) and has sufficient storage capacity to cater the buffer stocks across the supply chain.

(4) Distribution

The process of distribution can be categorized into major groupings of activities—the overall system design, including the different organizational levels; the supporting information systems (electronic and hard copy); inventory management; and both the transport and storage operations. Their collective objective is to provide a cost-effective distribution system that ensures a continuous supply of PHPs in a usable condition is made available to TB patients' and diagnostics centers.

- **Transport:** The movement of medicines from the initial port of entry to the national storage operations, through the provinces, to the districts, and on to the facilities requires detailed oversight.

NTP recommends safe, timely and quality assured delivery of PHPs from National level to PTPs and from Provincial TB Program to districts and onward supplies to health facilities.

(5) Usage of ATT medicines

- **Rational Use of ATT Medicines:** The concept of rational use in the context of pharmaceutical management is that patients receive correct medication and adhere to the treatment protocol. For details please refer to Drug Management Guidelines and Dispensing Manuals.
- **Pharmacovigilance:** The pharmacovigilance system for ATT medicines should be designed to detect, assess, understand, and prevent adverse effects, particularly the long-term and short-term side effects of medicines. The aims of pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines, thus encouraging safer and more effective use of medicines and a resolution of the sometimes apparently conflicting interests of public health and individual patient welfare. A comprehensive National guideline on Pharmacovigilance is in development phase and will encompass the subject in detail.

Management Support

Management support is located at the center of the PHPM cycle and is cross cutting activity. The roles of this core function are to review the current practice of the four components of the cycle (selection, procurement, distribution/storage, and use) comprehensively and to identify the weaknesses and invest necessary resources to overcome those weaknesses. From National TB Control Program to Provincial TB Control Program till district health authorities, each management cadre is responsible for its role in supporting the Pharmaceutical and Health Product Management.

Disposal of Expiries and Waste

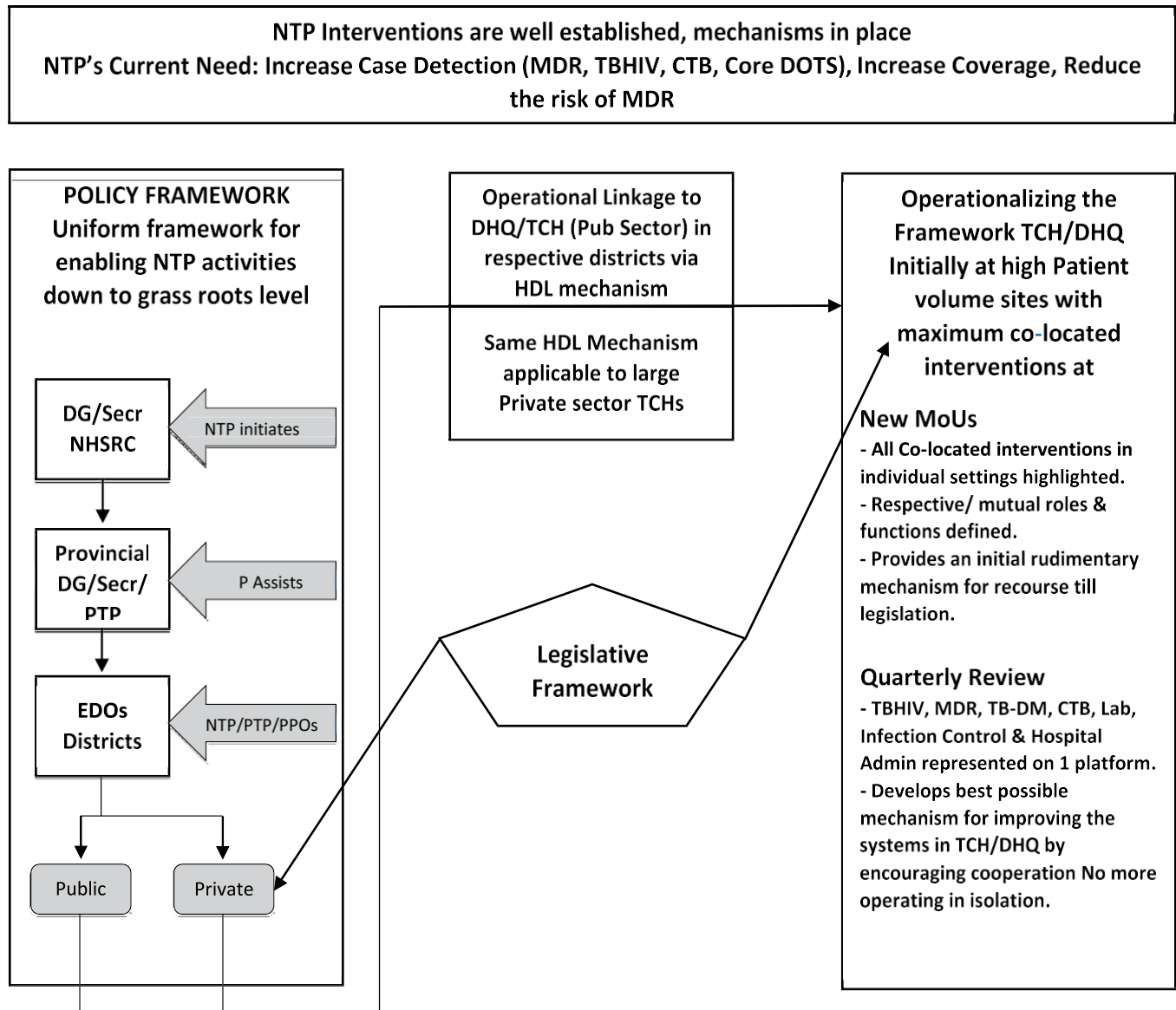
Once past the expiry date, ATT medicines become less efficacious and may develop a different adverse drug reaction profile. A number of methods exist for safe disposal of expired and wasted ATT medicines [20]. These methods involve minimal risks to public health and the environment. The main disposal methods suitable for ATT medicines are as follows:

- **Return to donor or manufacturer—**wherever practical, the possibility of returning unusable medicines for safe disposal by the manufacturer should be explored.
- **Incineration—**The NTP recommends purpose-built high-temperature incineration as the best environmental-friendly option for pharmaceutical destruction.
- **Landfill—**this implies putting waste directly into a land disposal site without prior treatment or preparation.

ANNEXES

Framework for Hospital DOTs Linkages

Framework for Hospital DOTs Linkages



SYSTEM-WIDE LINKAGES (HSS)

Building Synergies

Nutrition Department – Linkage to support MDR/Social Support intervention

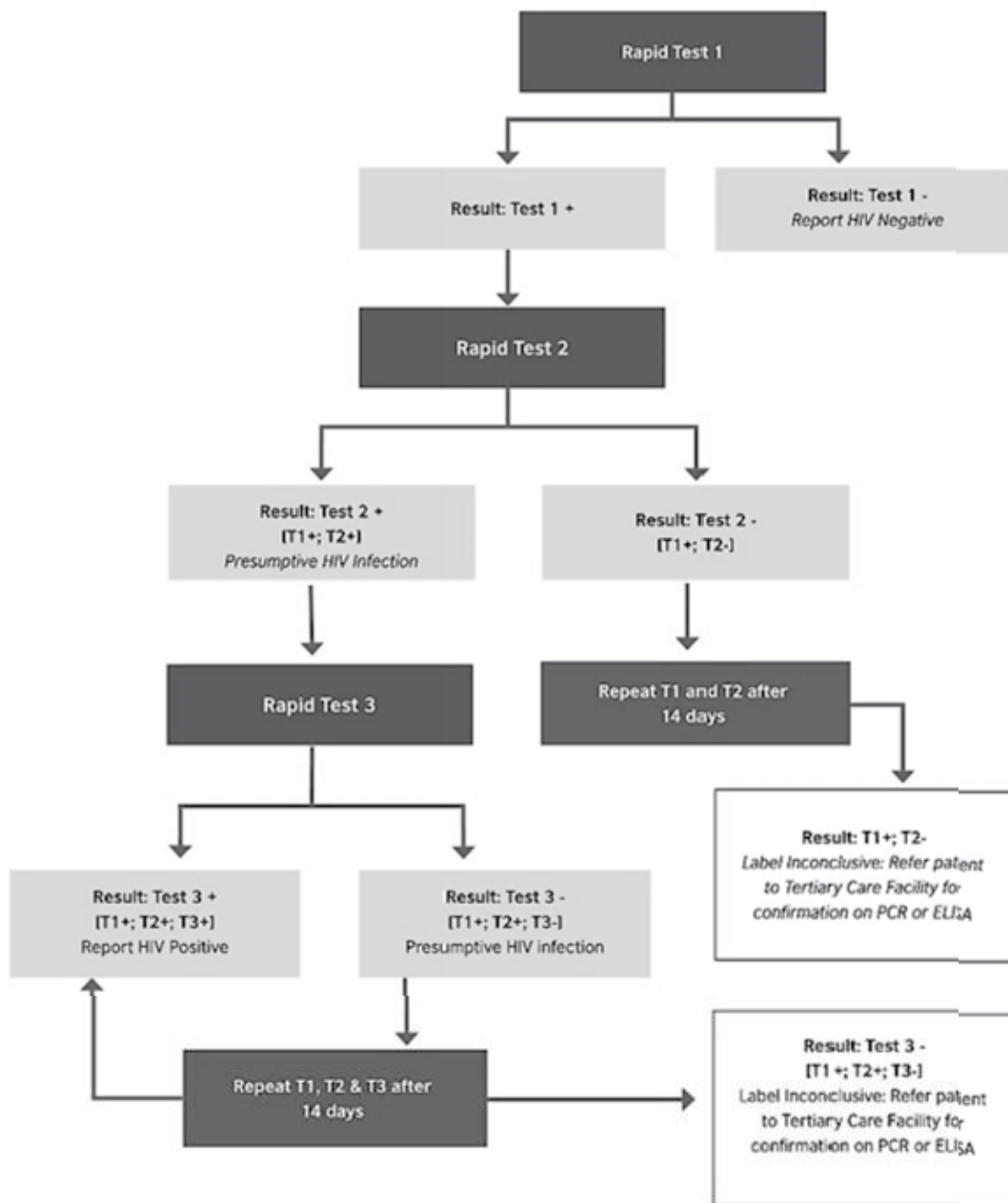
IHR – Cross-border Reporting mechanism, regional partnerships

NHIRC – Reconcile reporting systems with National System, encourage data use

Universities – Collaboration for research, internships, innovative solutions

Philanthropy – Define and actualize (including Legal.) mechanism for enabling such support from persons/organizations

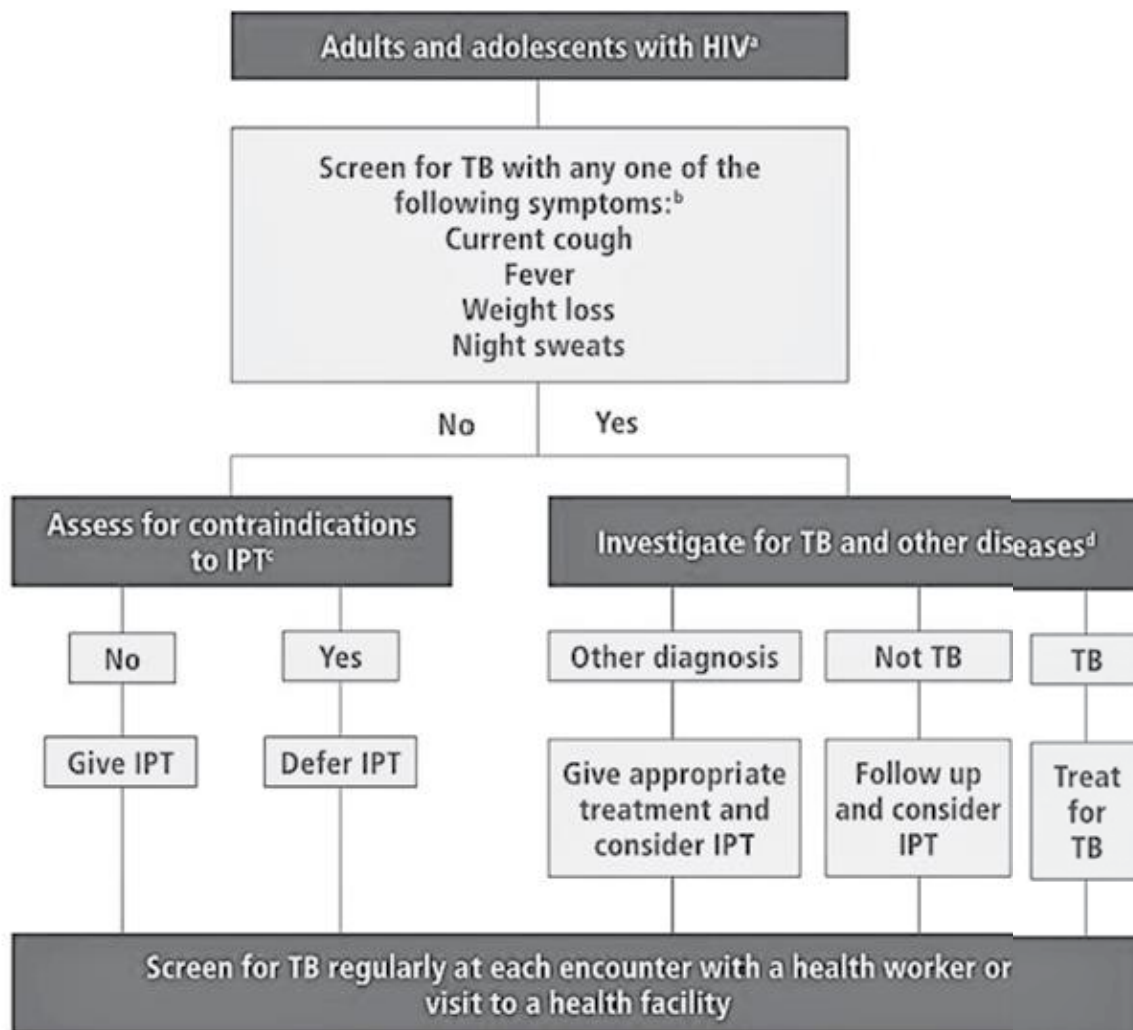
HIV (Three) Serial Rapid Test Algorithm



Recommended Rapid Tests²⁴

Test 1 = Alere Determine HIV-1/2 Ag/Ab Combo (Sensitivity > 99%)
 Test 2 = Uni-Gold HIV (Specificity > 99%)
 Test 3 = SD Bioline HIV-1/2 3.0 (Sensitivity > 99%, Specificity > 98%)

Algorithm for TB screening among adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



IPT: isoniazid preventive therapy

^a Every adult and adolescent should be evaluated for eligibility to receive antiretroviral therapy. Infection control measures should be given priority to reduce *Mycobacterium tuberculosis* transmission in all settings that provide care.

^b Chest radiography can be done if available but is not required to classify people into TB and non-TB groups. In settings with high HIV prevalence and a high TB prevalence among people living with HIV (such as exceeding 10%), strong consideration must be given to adding other sensitive investigations.

^c Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting isoniazid preventive therapy. Although not a requirement for initiating isoniazid preventive therapy, tuberculin skin testing may be performed as a part of eligibility screening in some settings.

^d Investigations for TB should be performed in accordance with existing national guidelines.

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