National Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis (PMDT)

Edition - 2020

National TB Control Program - Pakistan

Ministry of National Health Services, Regulations and Coordination
National TB Control Program
World Health Organization
USAID FROM THE AMERICAN PEOPLE

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Foreword

Pakistan stands 5th in terms of high burden of DRTB in the world with an estimated 25,000 drug resistant TB cases annually. This resistant form of TB needs special focus due to prolonged treatment, potential side effects and high mortality. National TB Control Program, since 2010 has taken measures to address this challenge by adaptation of WHO recommended interventions to establish and strengthen health systems to effectively manage the problem.

This guideline has been revised based on the latest WHO recommendations in June 2020 "Consolidated DRTB guidelines". NTP constituted a guideline development group comprising international and national panel of experts. Participation of all provinces and partners was encouraged in order to develop a consensus document.

The guidelines cover all important concepts related with DRTB however, the special focus is on all oral treatment (shorter and longer treatment regimens), lab diagnostic protocols, aDSM, isoniazid resistant TB and decentralization of DRTB management at district level among others.

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.

I hope these guidelines will go a long way in improving care of DRTB patient in the country.

I would also like to thank USAID and WHO for financial and technical support respectively and looking forward to work together in a participating environment in eradicating TB/DRTB from Pakistan.

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Acknowledgments

These guidelines were a revision and update of the National DR TB Guidelines 2019 including active TB drug-safety monitoring and management (aDSM), in view of WHO's new Consolidated guidelines on tuberculosis and WHO operational handbook on tuberculosis June 2020.

NTP nominated a core group as part of Guidelines Development Working Group Committee for revision process with the following members:

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Abbreviation & Acronyms

aDSM	Active TB Drug-Safety Monitoring and Management
AFB	Acid-fast bacilli
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
AST	Aspartate transaminase
ART	Antiretroviral therapy
B+ve	Bacteriologically confirmed (by smear microscopy and/or Xpert MTB/RIF and/or culture)
CNS	Central Nervous System
CPT	Co-trimoxazole preventive therapy
DOTS	Directly Observed Treatment Short-Course Strategy
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
ECG	Electro-cardiogram
EPTB	Extra-Pulmonary Tuberculosis
FBC	Full Blood Count
FDC	fixed-dose combination (medicines)
FLD	First-line drugs
FQ	Fluoroquinolone
HR-TB	Isoniazid resistant tuberculosis
(H)REZ	(isoniazid)–rifampicin–ethambutol–pyrazinamide
HIV	Human immunodeficiency virus
INH	Isoniazid
INH $_{Hh}$	High-dose INH
LJ	Lowenstein-Jensen
LPA	Line Probe Assay
LTR	Longer treatment regimen
MGIT™	Mycobacteria Growth Indicator Tube
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multidrug-resistant tuberculosis
MTBDRsl	GenoType Mycobacterium tuberculosis drug-resistant second-line assay
MUT	Mutation
NSAID	Non-steroidal anti-inflammatory drug
NTP	National Tuberculosis Program
NRL	National Reference Laboratory
PTB	Pulmonary tuberculosis
PLHIV	People living with HIV
QTcf	Corrected QT interval by Fredericia
RR-TB	Rifampicin-resistant TB
SAE	Serious Adverse Event
SLDs	Second Line Tuberculosis drugs
SLI	Second-line injectable
STR	Shorter treatment regimen
TAD	Treatment after default
TAF	Treatment after failure
TB	Tuberculosis
TSH	Thyroid-stimulating hormone
UV	Ultraviolet
WHO	World Health Organization
WT	Wild type (typical form as it appears in nature (different from mutation)
XDR-TB	Extensively drug-resistant tuberculosis

Abbreviations of TB Agents

Am	Amikacin
Amx-Clv	Amoxicillin–Clavulanic acid
Bdq	Bedaquiline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
Gfx	Gatifloxacin
Hh	high-dose isoniazid
H	Isoniazid
Imp-Cln	imipenem–cilastatin
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
PAS	*p*-aminosalicylic acid
Pto	Prothionamide
R	Rifampicin
S	Streptomycin
T	Thioacetazone
Trd	Terizidone
Z	Pyrazinamide

Section 1:

Introduction

Tuberculosis in Pakistan

Pakistan ranks fifth among high TB burden countries in the world. It is the country with the largest population (217 million) and number of TB cases in the Eastern Mediterranean Region of the World Health Organization. In 2019, there were 334 754 total notified TB cases, 81% of them pulmonary and 48 % of them bacteriologically confirmed. The estimated TB incidence was 263 per 100 000 population and the number of estimated incident case was 570,000. More than 200 000 TB cases are therefore estimated to be "missing" either not diagnosed or not reported to NTP. Many may be found in rural areas and in the unregulated private sector where efforts are made to strengthen notifications. About 42,000 persons are estimated to have died of TB in 2019, and another 1900 died of TB/HIV, although mortality according to the estimates has been decreasing since 2002[1] (annex 1 contains a list of major references in addition to the footnotes). The JPRM 2019, followed by the NSP and the currently planned GF project have all focused on UHC and access to care, through strengthening the PHC involvement in TB diagnosis and care and bringing the private sector to work more closely with the NTP.

Drug-Resistant Tuberculosis in Pakistan

Pakistan ranks fifth among high DR-TB burden countries in the world with an estimated 25000 RR/MDR-TB cases among estimated TB cases in 2019, 4.2% among new cases and 7.3% among previously treated cases. In the drug resistance survey in 2012-13, prevalence of RR was estimated at 4.2% in new and 18.1% among previously treated cases. Estimates in previously treated was recently reduced to 7.3% based on routine surveillance (annex 2). The number of DR-TB cases estimated from all notified TB cases, is around 13600 , while if estimated from notified pulmonary bacteriologically confirmed TB cases (by smear microscopy or Xpert) it is around 7300. Out of 3,820 laboratory confirmed RR cases in 2019, 3004 were enrolled on DR treatment. [1] Ensuring Xpert testing of all confirmed TB cases could add more than 2000 cases annually, while ensuring Xpert testing of all pulmonary notified cases would add more than 10 000 RR cases.

Notifications of RR-TB have increased gradually especially with the expansion of Xpert test, but the increase has been slow and there was a decline in 2019 (Figure 1). In 2019, 62% of bacteriologically confirmed pulmonary TB cases (smear and/or Xpert) had Xpert results: 59% in new and 89% in previously treated patients. Notifications are incomplete since the GXAlert system only covers 2/3 of laboratories, while some cases are duplicated. See also section 3 Case finding and laboratory. The rate of bacteriologically confirmed TB (by smear and/or Xpert) was 59 per 100 000 in 2019, highest in Punjab and Sindh that had very similar level, but the rate of RR patients enrolled on treatment was twice as high in Sindh as in Punjab (Table 1). Less than two thirds of enrolled patients are successfully treated (Figure 1). More information on treatment result are found in Section 4 Treatment regimens.

[1] Data for 2019 provided by NTP to WHO August 2020

Figure 1: Notified and enrolled RR-TB patients 2015-2019 and successfully treated (2015-2017) (from ENRS)

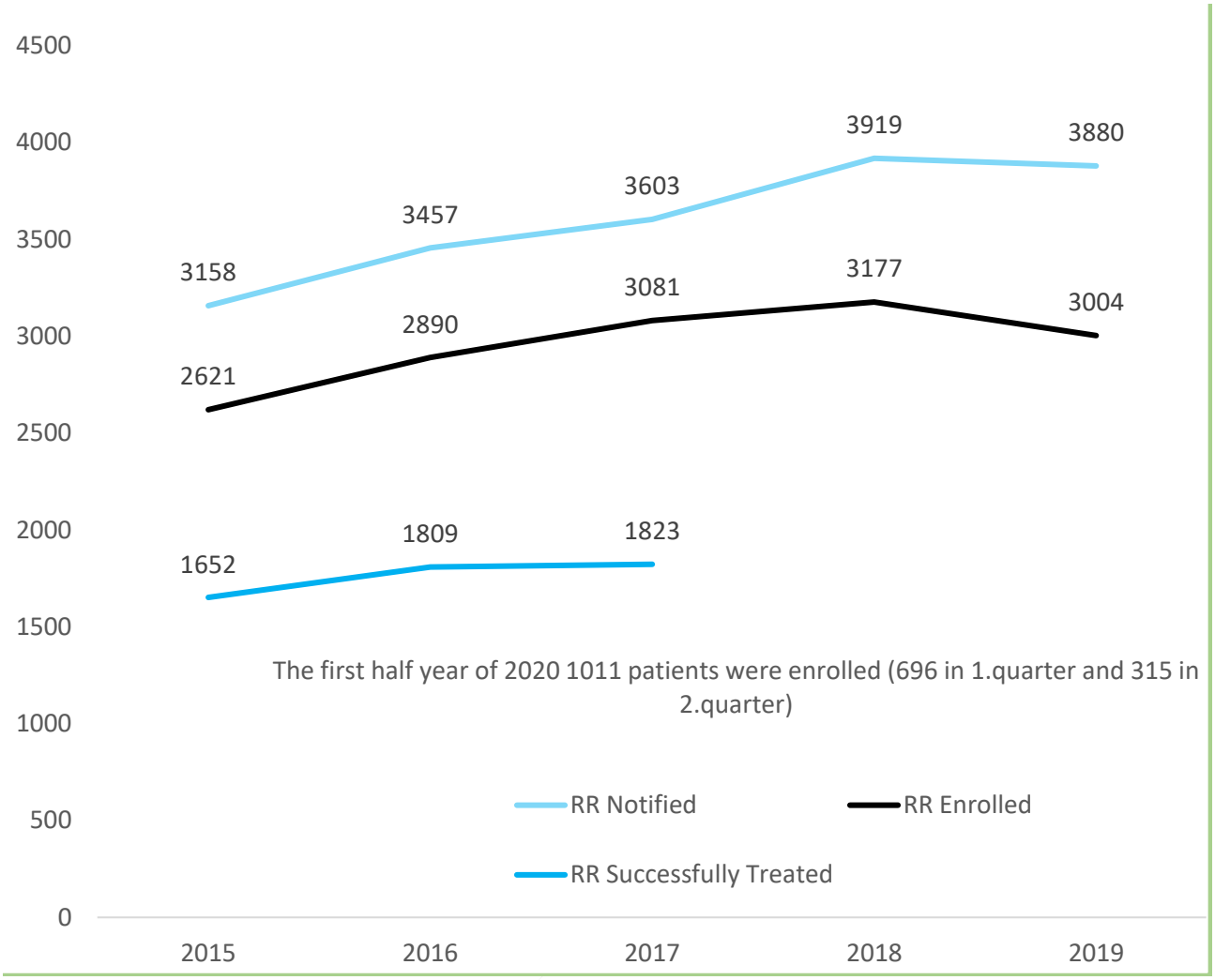


Table 1 RR-TB enrolment by province/region 2015-2020 and rate per 100 000 populations of confirmed TB and enrolled RR by region 2019

A. RR-TB Enrolment (numbers)								
Year	Punjab	Sindh	KP	Balochistan	Islamabad (ICT)	Gilgit Baltistan	Azad Kashmir	Total
2015	1037	1146	277	85	37	4	30	2616
2016	1215	1233	222	97	31	4	31	2833
2017	1317	1309	250	95	33	2	30	3036
2018	1374	1275	339	63	51	6	29	3137
2019	1447	1156	299	85	45	1	11	3044
2020 2Qs	500	372	98	27	10	0	4	1011
B. Rate per 100 000 population of confirmed TB and enrolled RR by region 2019								
Confirmed TB	66,2	67,2	38,7	33,3	21,5	25,7	53,1	59,0
Enrolled RR-TB	1,3	2,3	0,8	0,6	2,2	0,1	0,3	1,4

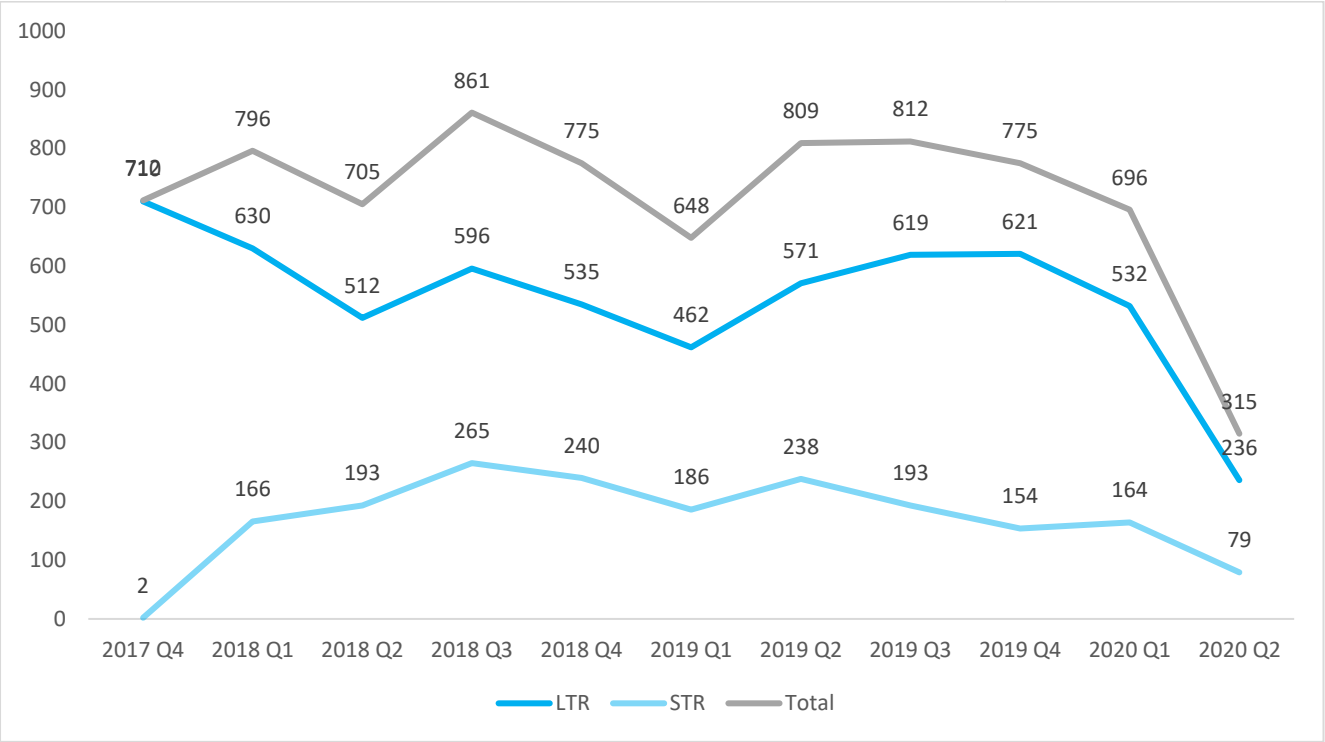
The percentage of RR in TB cases in Pakistan is high but not very different from other countries in EMRO, but the remarkably higher percentage with resistance to fluoroquinolones (FQ), the most important drugs to treat RR, is a grave concern - 37% in 2019, although a gradual decline was seen compared to previous five

years, across all provinces. In 2019 the lowest FQ resistance was reported in KP province (27%), stable around 30% in Sindh and highest in Punjab (43%). (See Annex 3 with trend of FQ resistance in provinces 2013-2019).

Although there are provincial regulations to control over the counter sale of anti-TB drugs, there is still rampant sale and use of these medicines without prescription. Tuberculosis drugs are available in private pharmacies and the private sector is often not linked to the TB Program. These medicines may therefore be used incorrectly thereby contributing to the generation and expansion of drug resistance. The current GF project includes concrete actions to ensure compliant prescription practices and a monitoring of TB medicines' sales. **120,000** additional cases are expected to be notified through this intervention in three years which is most cost effective intervention proposed in the grant. FQs and Lzd are currently widely used for respiratory infections, which contributes to creating resistance.

The 2020 covid-19 pandemic also affected TB and DR-TB, with dramatic decline in enrolled patients (Figure 2).

Figure 2 Number of enrolled RR-TB patients 4.quarter 2017-2.quarter 2020 by regimen (STR and LTR)

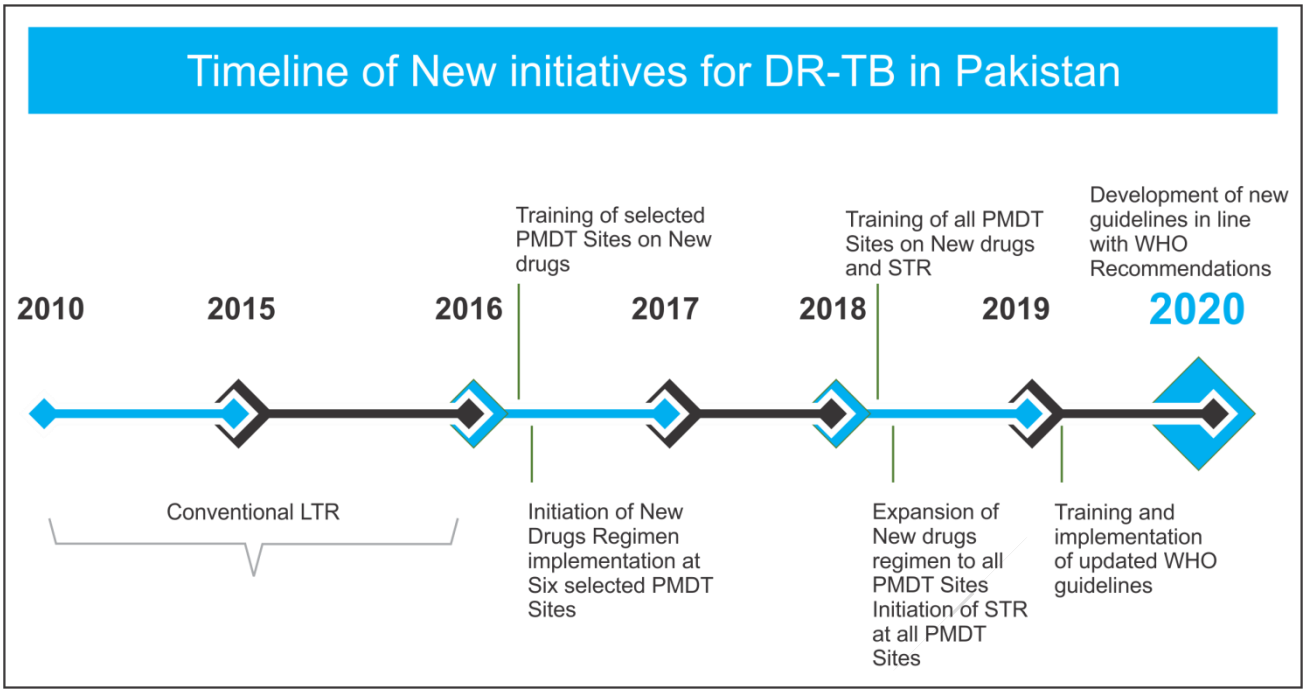


Development of PMDT Treatment Sites and Current Challenges

In 2009 Pakistan was approved through the GLC mechanism to start treatment for 400 MDR-TB patients. Programmatic management of drug resistant TB (PMDT) was piloted in three hospitals in 2010 through Global Fund support. All 33 PMDT Treatment Sites have been providing treatment for DR-TB patients in all provinces and regions (Table 2). These treatment sites are public or private and their PMDT work is coordinated and supported by the National TB Control Program (NTP) in collaboration with the Provincial TB Control Programs (PTPs). Through PPM projects an increasing proportion of DR-TB patients are referred from the private sector to Xpert laboratories and PMDT Treatment Sites.

Initially the conventional Long Term Regimen (LTR) of two years was used and with subsequent changes in the WHO and National guidelines, the changes were implemented at all treatment sites accordingly.

Figure 3 Timeline of new initiatives for DR-TB in Pakistan



Bedaquiline (Bdq) regimen was first introduced in 6PMDT Sites in 2016, and expanded to all Sites in 2018 along with introduction of Short Term Regimen (injection based). In 2019, WHO updated guidelines and rapid communication and the National DR-TB Guidelines were updated and implemented in all PMDT Sites. The all oral Short Term Regimen was introduced in February 2020 after its endorsement by the WHO and Technical Working Group (STAG) in Pakistan (Figure 3).

A major challenge is the slow increase in detection and enrolment of RR patients, in spite of rapid Xpert expansion. The current centralized model of PMDT Site is based on a dedicated PMDT Team provided through Global Fund. Treatment and management of RR-TB is expensive, prolonged, and associated with multiple adverse effects. These factors have contributed to poor patient adherence further increasing prevalence of DR-TB. The treatment success is low (65% in 1.half of 2018) although the declining trend has stopped. Main challenges are high death rate and LTFU and the failures (tables in Section 3 and annex 5). Deaths are most likely caused by patients presenting too late for TB diagnosis due to lack of access and that health facilities are not alert enough in detecting presumptive TB and ensuring lab investigation. LTFU is probably linked to the long distance to PMDT sites which usually covers 3-4 districts. Therefore, PMDT Treatment Sites are being (gradually) decentralized to all districts (see Section 2).

Table 2 List of PMDT sites (by province/region) and implementing partner 2019 (from NTP Annual report 2019 table 15)

Province / Region	PMDT Sites		
	#	Name of PMDT Site	Public/Private
AJ&K	1	AIMS Hospital, Muzaffarabad	Public
Balochistan	1	Fatima Jinnah Hospital, Quetta	Public
	2	DHQ Hospital, Loralai	Public
Gilgit Baltistan (GB)	1	DHQ Hospital, Gilgit	Public
Islamabad (ICT)	1	PIMS Hospital, Islamabad	Public
Federal	1	Military Hospital, Rawalpindi	Public
Khyber Pakhtunkhwa	1	Lady Reading Hospital, Peshawar	Public
	2	Ayub Teaching H-Abbottabad	Public
	3	MMC-Mardan	Public
	4	MMMTH, Dera Ismail Khan	Public
	5	SS Teaching Hospital, Swat	Public
Sindh	1	Ojha Chest Hospital, Karachi	Public
	2	DHQ Hospital, Mithi	Public
	3	Chest Unit, JPMC, Karachi	Public
	4	Chest Diseases Hospital, Kotri	Public
	5	DHQ Hospital, Mirpurkhas	Public
	6	PMC Hospital, Nawabshah	Public
	7	CMC Hospital, Larkana	Public
	8	GMM Civil Hospital, Sukkur	Public
	9	Indus Hospital, Karachi	Public
	10	Delhi Medical Center, Karachi	Private
	11	Red Crescent Hospital, Hyderabad	Private
Punjab	1	Mayo Hospital, Lahore	Public
	2	Jinnah Hospital, Lahore	Public
	3	DHQ Hospital, Faisalabad	Public
	4	DHQ Hospital, Sialkot	Public
	5	DHQ Hospital, Sargodha	Public
	6	Nishtar Hospital, Multan	Public
	7	BV Hospital, Bahawalpur	Public
	8	SZ Hospital, Rahim yar Khan	Public
	9	Samli Hospital, Murree	Public
	10	Gulab Devi Hospiatl, Lahore	Private
	11	Leprosy Hospital, Rawalpindi	Private

Factors like proper diagnosis and infection control measures, correct DOTS implementation, precise treatment prescription by well-trained health care providers, and comprehensive social support for the duration of the treatment are some of the important steps to bring the high burden of DR-TB in Pakistan.

The PMDT sites are strengthening infection control for outpatient, inpatient DR-TB care including second line drug procurement and management, establishment of guidelines, training for senior and mid-level doctors, paramedics, and laboratory staff, comprehensive community-based DR-TB care and social support for patients and treatment supervisors through links with DR-TB clinics in public as well as private sector.

Development of resistance

Drug resistance is man-made. It usually occurs due to inadequate treatment such as inappropriate regimens (such as treatment with a single drug), use of lower-than-recommended doses, poor drug quality and poor

adherence to treatment (Figure 4). TB bacilli spontaneously mutate, but resistant strains develop if TB drugs imposes selection pressure on MTB populations, resulting in reduction in drug susceptible bacilli, the advantageous reproduction of drug resistant mutants and the emergence of drug resistance: this is acquired resistance; implying that resistance emerges during the treatment. On the other hand, primary resistance refers to patients infected with resistance stain strain before having any anti TB treatment. Mostly, a mutation cause resistance to only one or a group of drugs. Resistance to two or more drugs occurs due to sequential mutation in different genes.

Figure 4 Causes of resistance:*

Health care providers: inappropriate treatment(Regimen)	*Drugs: inadequate supply/quality*	*Patients: inadequate drug intake or treatment response*
Inappropriate guidelines	Poor quality	Lack of information
Non-adherence or non-acceptance of guidelines	Unavailability of some drugs (stock outs)	Lack of means to adhere To treatment (transportation, food, etc.)
Absence of guidelines	Poor storage conditions	Social, economic barriers and Myths
Poor training	Inappropriate dosage or combination	Adverse events (AEs)
Lack of treatment monitoring	Poor regulation of medicines	Inadequate directly observed treatment (DOT)
Poor management of adverse drug reactions		Poor absorption of drugs
Poorly organized or funded TB control programs		Substance abuse/dependency
Treatment outside the program		

**ref. Field Guide for the management of DR-TB. The Union 2018 (adapted from the Companion Handbook to the WHO Guidelines for PMDT. WHO/HTM/TB/2014.11)"*

The most important question to ask about drug resistance, is where it came from. Was it primary, or was it acquired? The significance of the distinction is that primary drug resistance indicates a need for better TB control to interrupt transmission, whereas acquired drug resistance indicates a need for better patient management to prevent the evolution of resistance. The main objective of TB control is to stop transmission by early detection of infectious patients without creating drug resistance.

A simple way to make this distinction is by referring to the history of care. If a patient has not been treated before, drug resistance is often assumed to be primary and the result of transmission. If a patient has been treated previously, drug resistance is often assumed to be acquired. However, studies have shown that transmission of resistant strains also play a role among people with previous TB treatment, not only among treatment-naive persons. In areas with high rates of TB, getting infected with a resistant strain rather than acquisition accounts for almost two thirds of incident DR-TB in previously treated individuals.

Thus, RR in TB patients can be due to 1) new patient infected with primary drug resistance, 2) reinfection with exogenous resistant strains, or 3) acquired RR during the course of treatment.

Definitions in DR-TB

Types of Drug Resistance – by drug

- **Mono-resistant TB:** resistance to one first-line anti-TB drug only.
- **Poly-drug-resistant TB:** resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.
- **Multidrug-resistant TB (MDR-TB):** resistance to at least both isoniazid and rifampicin.
- **Rifampicin-resistant TB (RR-TB):** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.
  The majority of the RR-TB cases detected among retreatment cases are also resistant to isoniazid. Currently available tests (Xpert® MTB/RIF) enable relatively easy detection of R-resistance but not H-resistance. RR-TB cases are therefore treated as MDR-TB.
- **Extensively drug-resistant TB (XDR-TB):** resistance to any fluoroquinolones (FQs) and to second-line injectable (SLIs) (amikacin), in addition to multidrug resistance.
- **Pre-extensively drug-resistant TB (pre-XDR-TB):** resistance to any FQ or to SLI (in addition to multidrug resistance. NB: Although this use of the definition for pre-XDR-TB is widespread, it is not officially recognized.
- **DR-TB patients**. Any patient who falls into one of these categories of drug resistance is considered a DR-TB patient.

In these guidelines we usually talk about DR-TB (since there is a section on INH-TB) or RR-TB.

DR-TB treated only with first line drugs?

The guidelines recommend that patients infected with strains with relatively simple resistance patterns (H, HS, HE and HZ) and who are not treated with second line drugs, stay in the District BMU Tuberculosis Register, where a modified short chemotherapy course can be provided (for more information please refer to the Section on INH resistance (some INH resistant patients are treated with FQ) and The National Guidelines for Tuberculosis control in Pakistan). Patients infected with more complicated mono- and poly-resistance strains (involving Rifampicin Resistance) should be treated at PMDT site and recorded in PMDT R&R tools.

Category of DR-TB by previous treatment

- Resistance among new patients: resistance in patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month. (National guideline 2019)
- Resistance among previously treated patients: resistance in patients who have undergone anti-tuberculosis treatment for >1 month. These patients are usually grouped into relapses, after failure and after LTFU – according to the result of the previous treatment. Sometimes this result is unknown and the patient classified as such. In addition, some patients have sputum collected at 2, 3, 4 months or later during STR or LTR treatment usually because of positive smears. Most will not have failed yet. It is useful to assess the resistance pattern (especially resistance to Rif and Fq in these groups separately to see if there is need to modify treatment regimens.

Presumptive RR-TB patients

Patients who are most at risk of having RR-TB and should have an Xpert test, such as:

- Previously treated patients
- Individuals with TB symptoms who are contacts of patients with known RR-TB
- Other groups – see Section on Case finding

Contacts

- **Household contact**: individuals sharing living space for one or several nights or spending several hours a day with the index case during the 3 months before the start of treatment of the index case.

- **Close contact**: individuals sharing living space for prolonged periods during the 3 months before the start of treatment of the index case (places of social gathering, work, institutions).
- **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
- ***Note: Symptomatic contacts*** *of patients with RR-TB should undergo diagnostic tests for RR-TB without delay. A contact of an infectious case (index case) is at high risk of infection and should be investigated systematically and actively for MDR-TB.*

Treatment outcomes in STR

The outcomes of STR are defined as follows (the first of these event to occur):

- **Cured**: treatment completed without evidence of failure and 2 consecutive cultures taken at least 30 days apart are negative in the continuation phase.
- **Treatment completed**: treatment completed without evidence of failure but there is no record that 2 consecutive cultures taken at least 30 days apart are negative in the continuation phase.
- **Died:** A patient who dies for any reason during the course of treatment.
- **Failure**:
    - a patient who has a positive culture after ≥6 months of treatment (except for an isolated positive culture, which is a culture preceded by ≥1 and followed by ≥2 negative cultures) or,
    - a patient who after an initial conversion, has a reversion after ≥6 months of treatment with two consecutive positive cultures taken at least 30 days apart or,
    - a patient who has 2 consecutive positive smears with a degree of ≥2+ after ≥6 months and no improvement in clinical condition (in settings with limited access to sputum culture) or,
    - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs or,
    - treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of adverse drug reactions. Adding two drugs is classified as failure while dropping two drugs is not.
- **Lost to follow-up**: A patient whose treatment was interrupted for ≥2 consecutive months.
- **Not evaluated:** A patient for whom no treatment outcome is assigned (this includes patients "transferred out" to another treatment unit and whose treatment outcome is unknown).
- **Treatment success:** The sum of cured and treatment completed.

Assessing relapse rate

Relapse: patient who has been treated for RR-TB, has been declared "cured" or "treatment completed" and who is diagnosed with another episode of confirmed RR-TB usually during a follow-up period of one year. (Early relapse within 2 years, late relapse after 2 years) National guideline 2019

Treatment outcomes of patients on LTR

There are seven outcomes for MDR TB which are based on laboratory smear and culture as monitoring tools. The outcome categories correspond to the outcome categories for drug susceptible TB (Table 3).

Table 3 MDR Treatment Outcomes for LTR

Cured	Treatment completed as National policy (minimum 18 month with 16 months past culture conversion) without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative (after intensive phase in cases where injectable is used)
Treatment completed	Treatment completed as recommended by National Policy (minimum 18 months with 16 months past culture conversion) without evidence of failure BUT no record that

	three or more consecutive cultures taken at least 30 days apart are negative.
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • Lack of conversion[1] by the end of the intensive phase; or • Bacteriological reversion[2] in the continuation phase after conversion to negative; or • Evidence of additional acquired resistance; or • Adverse drug reactions[3]
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
Not evaluated	Patient for whom no treatment outcome is assigned. (This includes "transferred out[4]" to another treatment unit and whose treatment outcome is unknown).
Treatment Success[5]	A patient who either was cured or completed treatment

1. Conversion: (to negative): Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative Culture is used as the date of conversion.

2. Reversion: (to positive): Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, is found to be positive. For the purpose of defining Treatment failure, reversion is considered only when it occurs in the continuation phase.

3 When treatment is interrupted to manage side-effects the treatment is declared a failure:

If patient has life threatening side-effects requiring removing two or more drugs.

If control of side-effect is not possible and treatment regimen not appropriate after removal of causal agents.

If a clinical decision has been made to terminate or change treatment (addition of two classes of anti-TB drugs).

4. Patients who have transferred in should have their outcome reported back to the treatment center at which they were originally registered. The responsibility for reporting their final outcomes rests with the original treatment center. Note that the category "Transferred out" (referring to a patient who moved to another treatment center but whose definitive outcome at the end of treatment was not established) may inform the programmer manager about patient mobility, but is not an outcome of treatment.

5. Total number of patients who succeeded treatment (total cured patients+ total treatment completed patients) will be used as numerator to calculate Treatment Success Rate (TSR) of Programmatic Management of Drug Resistant TB (PMDT).

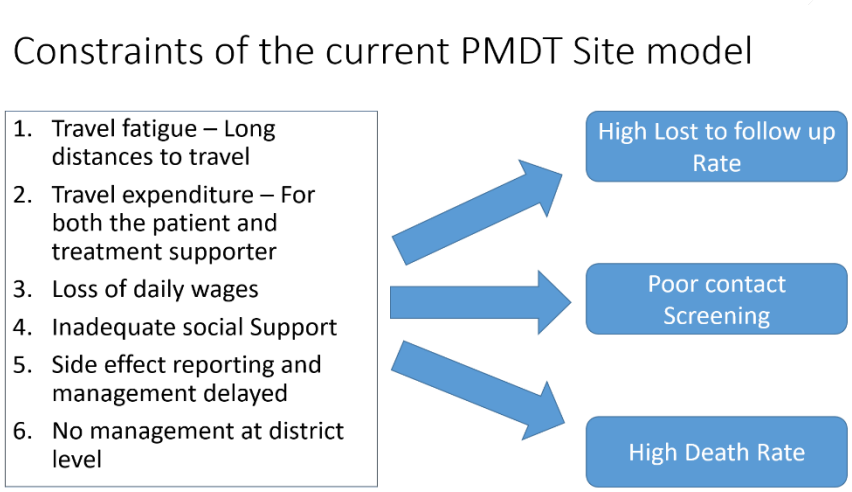
Section 2:

PMDT Levels and Decentralization

Decentralized DRTB care: Constraints in the current Centralized DR-TB Management model

The current centralized PMDT approach was based on provision of care to DR-TB patients through highly trained staff. Specific rooms were allocated from the relevant hospital administration which were renovated through Global Fund keeping in view the required infection control measures... This model could, however, only guarantee establishment of PMDT Sites in 26 districts out of 154 throughout Pakistan - a coverage in 17% of the districts. Each PMDT Site is attached to 4-5 districts from where the patient has to travel in order to get DR-TB services. The baseline and follow up tests including sputum microscopy, blood tests, radiology etc. were provided through the hospital whereas the Sputum culture and Drug Susceptibility testing was provided through specialized laboratories (National and Provincial Reference Laboratories) where sputum samples were transported through courier service.

Figure 5 Constraints of the current PMDT site model



Gap Analysis done in 2019 at the National and Provincial Levels revealed that diagnosis and registration was high in districts where PMDT Sites were established whereas districts without established PMDT Sites had a much lower DR-TB detection rate. This finding indicates that the availability of DR-TB management services sensitized doctors and paramedics in the districts regarding DR-TB and contributed to increased detection and early treatment start.

Figure 6 Comparison of Registration between districts with and without established PMDT Sites

The challenges with the Centralized Model are (see also Figures 5 and 6):

1. The patients in the centralized PMDT model have to travel long distances to different districts each month for follow up. This increases travel fatigue, travel cost, loss of daily wages, not only for the patient but also for the accompanying Treatment Supporter. Seeking care from untrained physicians may amplify the pattern of resistance. The travel cost also includes food cost, night stay cost and other miscellaneous costs. Finally, the undetected and untreated patients may also spread infection to the other exposed contact around.
2. The social support currently given in this scenario is minimal and does not even cover one-way travel for one person. Each patient is provided with PKR 1000/ Month for Social protection and PKR 600/ Month as travel cost while each Treatment Supporter is provided with PKR 600/ Month as travel cost. All payment is done through Easy Paisa system.
3. With PMDT Sites in different districts, the patients fail to report the side effects timely leading to sequelae. ADR management is therefore either delayed or not done.
4. Inability of PMDT Site to manage the side effects (due to delayed reporting as mentioned in point 4) also leads to mistrust of patient on the treatment and ultimately high lost to follow up rate.
5. The long distance travel in local transport also increases the risk of spreading infection. The buses, trains or other means of transport are closed environments making the other travelers at high risk of acquiring DR-TB infection.

Levels of PMDT

PMDT refers to Programmatic Management of Drug Resistant TB. This means that the management of Drug Resistant TB is done according to specified protocols and guidelines by trained staff. PMDT not only entails the clinical aspect of the DR-TB management, but also includes programmatic and administrative aspects. The management of DR-TB patients is, therefore, not only done at the health facility level but is also overseen by National, Provincial and District Level teams. Some of these aspects have been discussed below.

Central Level

In the post devolution scenario, roles and responsibilities at central level are revised especially focusing more on capacity building and provision of technical expertise at provincial level. The revised roles and responsibilities at central level includes establishment of norms and procedure for DRTB, development of national policy (country context and in line with WHO recommendations) for adoption at provincial level, development of training curricula and provincial capacity building, provision of technical expertise in reference to difficult to manage DRTB cases, monitoring and evaluation of programmatic component with provision of feedback, advocacy for improved community DRTB care, provision of quality based diagnosis services and establishment of liaison with other vertical programs (HIV) for improved DRTB diagnosis and effective coordinated treatment.

Provincial Level

The roles and responsibilities at Provincial level, which comprises of Provincial TB Control Program along with the Provincial Reference laboratories, includes establishment of norms and procedures for the control of DR TB, plan & assess needs, monitor, and evaluate the program, advocate for community care, integration with DSTB, ensure un-interrupted supply of diagnostic logistics (Xpert kits, R&R Tools etc.), capacity building of monitoring staff and the staff managing patients directly, provide Human resource, coordinate operational research on community care, organize and regularly supervise TB and DR TB diagnosis and treatment, coordinate with the central level, other institutions, e.g., NGOs and patient support systems, develop a specimen transport system in collaboration with the district teams, integrate DR TB with other services, e.g., HIV and maternal services, make linkages between PMDT Sites with culture labs & between peripheral labs with Peripheral Lab, provide DST services in collaboration with the National Reference Lab and ensure free of cost and un-interrupted treatment for the patients.

District Level

The roles and responsibilities at District level (District Health Management Team), which includes Chief Executive Officer, District Health Officer (Preventive Services), District TB Coordinator, District Laboratory Supervisor etc., includes supervision of the DR-TB management sites in the districts, ensuring all DR-TB detected patients are enrolled at the relevant PMDT Sites, development of linkages between PMDT Sites and Gene Xpert labs, development of specimen transport system within the district, advocacy within the district,

coordination with Provincial teams, identify hot spots in the district, rectification of administrative issues in collaboration with health facility administrations, assisting in patient retrievals and contact screening.

Role of Private Partners

In Pakistan, 86% of people use private sector for seeking health care whereas only 5% of private GPs are under NTP coverage with recommended guidelines and standard care in place.

The network of general practitioners who complies with National TB guidelines are successfully identifying and notifying TB cases as per national standards. As practice in vogue, a selected group of pulmonary TB patients (majority retreatment cases) are referred to nearest facility for Xpert testing which could be within the same vicinity or at times located at distances. In addition to location of Xpert site at distant areas to the referring GP, inadequate sputum referral system poses huge problems in diagnosis and enrolment of DRTB patients at the PMDT site.

Their role can be further enhanced in improvement in patient referral, DOT and timely management of adverse events through aDSM. The capacity of the GP should be built on the above-mentioned areas.

Under current circumstances, there is potential for improvement of linkage with the public sector:

1. Expansion in private sector coverage: Increase in number of GPs and accredited labs to improve diagnosis of DS-TB & DR-TB.
2. Improvement in sputum transport mechanisms to Xpert sites

PMDT SITE CENTRAL

"PMDT Site Central" are the current 33 PMDT sites. The Staff consists of: (see figure below)

- DR TB Clinician
- Pharmacist
- Psychologist/counsellor
- DOTs Facilitator – Social Support
- DOTS Facilitator Case Management Laboratory assistant
- Treatment coordinator
- Data Assistant

Roles and responsibilities

• Diagnosis of DR TB, ensure quality of treatment, prescription, and initiation, and clinical follow-up during treatment.
• Manage in-patients with severe disease and complications from treatment.
• Coordinate with respective District PMDT sites and provide technical support.
• Coordinate with clinical, data, and pharmacy staff.
• Provide laboratory services for DR TB patients, including screening tests for side effects.
• Maintain database (register) of all DR TB patients (ENRS).
• Keep track of follow-up appointment dates for all DR TB patients.
• Store outpatient records of all DR TB patients.
• Produce timely reports according to the national guidelines.
• Manage second-line drug stock (inventory, forecasting, and drug supply) for the region/district.

PMDT SITE DISTRICT

"PMDT Site District" are the future sites at district level implementing PMDT functions, with two models, see below. The staff includes:

- DR-TB Physician
- Laboratory Technician
- Data clerk
- DR-TB Treatment Supporter

Figure 7 Team Layout – PMDT site

Team Layout – PMDT Site

MDR-TB Physician

- Clinical evaluation
- Regimen selection
- Supervision of PMDT Team
- Linkage within hospital
- Attending IDMs for Linkages with districts

Pharmacist

- SLD Storage
- SLD demand
- SLD Dispensation to patient
- TS training
- Dose adjustment
- Pharmacovigilance

Psychologist

- Baseline psychological assessment
- Monthly assessment
- Group therapy
- Counseling on medicine adherence
- Infection control counseling

Treatment Coordinator

- Home Assessment
- Close contact screening
- Linkages with BMUs
- Linkages with districts
- Linkages with Xpert site
- Patient retrieval

DF- Case Management

- Management of patient files
- Ensure lab tests
- Monthly follow up list

DF- Social Support

- Maintaining monthly social support list
- Facilitating patients with Easy Paisa shops
- Maintaining social support record

Data Assistant

- Data entry into DR-TB 03 (Soft & hard)
- Monthly reporting
- Quarterly reports

Lab Attendant

- Sample collection
- Sample submission to lab
- Report collection
- Maintaining DR-TB 04 (hard and soft)
- Accompanying patients to various departments if needed

PMDT SITE DISTRICT:

Roles and responsibilities

- Clinical follow-up during treatment.
- Coordinate with respective PMDT sites.
- Coordinate with clinical, data, and pharmacy staff.
- Provide laboratory services for DR TB patients.
- Keep track of follow-up appointment dates for all DR TB patients.
- Store outpatient records of all DR TB patients.
- Manage second-line drug stock (inventory, forecasting, and drug supply) for the district.
- Coordinate with the DR TB physician of central PMDT for management of patient.
- Coordinate clinical support services.
- Coordinate with the treatment coordinator.
- Supervise the activities of treatment supporter

Table 4 Activities performed at PMDT sites (Hub and Spoke Model)

SERVICES	PMDT CENTRAL	PMDT DISTRICT
Clinical service	▪ Diagnose, Registration and enrollment ▪ Indoor service ▪ Outcome	▪ Monthly Follow up ▪ Side effects & Complication management
Lab service	▪ Smear ▪ GeneXpert & LPA ▪ Culture & DST ▪ Routine, Baseline & Special LAB investigations ▪ ECG, Audiometry &X-ray	▪ Smear ▪ Routine LAB investigations
Drug supply service	▪ Drug supply chain management ▪ Storage & Dispensing of drugs ▪ Pharmacovigilance	▪ Storage & Dispensing of drugs ▪ Pharmacovigilance
Social support service	▪ Disbursement through easy paisa ▪ ATM wallet ▪ Record keeping and communication	▪ Follow support services
Field visits	supervise treatment coordinator regarding	▪ Regular field visits of treatment coordinator ▪ Treatment adherence, ▪ Contact screening, ▪ Retrieval of missing cases / lost to follow up cases

Peripheral Level (BMU)

RR-TB patients should come weekly to their nearest BMU together with their treatment supporter. BMU staff ensuring that RR-TB patients are followed up properly include:

- Doctor/MO
- DOTS facilitator
- Paramedic/HCWs
- Outreach Teams (Lady Health Workers)

Roles and responsibilities at BMU

- Expedite the process of the visit to the clinic, Prioritize MDR-TB patients who should not wait in line.
- Review the record, drug-intake compliance during the last week, and guide accordingly
- Conduct a brief clinical assessment to make sure that the patient is doing well and continues to take the medications regularly
- The doctor, during clinical assessment, will make sure that any symptom or sign indicative of drug side effects is identified and managed as per NTP case management guidelines.
- In case minor or major side effects the doctor at BMU/DOTC center will record/update in TB01 card and will prescribe ancillary medicine and for moderate to severe side effects/adverse events will contact and refer the case to the PMDT site for further management.
- The DOTS center staff reminds the patient to visit the PMDT Treatment Site for monthly follow up visit.
- Make sure the necessary arrangement for contact screening and supervise the activity of treatment supporter.
- To take active measures on the earliest retrieving of non-adherent and lost to follow up patients.

Decentralization of DR-TB Care – "Hub and spoke" and "Complete decentralized" models

Each province has proposed a different model of decentralization but all models aim towards enabling at least one health facilities in all the districts to detect, treat and manage the DR-TB cases thus ultimately achieving 100% DR-TB treatment coverage throughout the country. There are two main models:

1. **Hub and spoke model:** designed by the Provinces of Sindh, KPK and Balochistan in which the existing PMDT Site will be responsible for initial assessment and enrollment of the patient. The decentralized site will comprise of staff from the hospital. The patient will then be referred back to his/her district where the patient will receive monthly treatment. In case of difficult to manage conditions or requirement of expertise, the patient will be referred back to the central PMDT Site; hence the decentralized sites will act as satellite sites of the central PMDT Site.

2. **Complete Decentralized Model;** designed by the Province of Punjab in which the patient after diagnosis will be completely managed by the decentralized site without having to travel to the central PMDT Site. The staff will be provided by the DHQ hospital. Two Paramedic staff; one for the facility and one for field activities have been proposed by the Program to facilitate the management of DR-TB patients and ensure complete and timely Recording and Reporting. In case of difficult to manage conditions or requirement of expertise, the Physician at the decentralized site will contact the pre-defined Technical review panel as described below, with all relevant clinical information of the patient. If required, the patient may travel to the central PMDT site. In this model the decentralized sites will be independent and not act as satellite sites of the central PMDT Site.

In both scenarios the patient care will be managed by trained district chest specialists and the District headquarter hospital teams. All the provinces plan to continue with the existing PMDT Sites and expand decentralization to all districts in next three years in phases.

The duties of the hospital staff in the decentralized model:

The management of DR-TB patients will be done at the District Head Quarter Hospitals who will provide the staff. Following roles will be carried out at the different levels in the district:

Table 5 The duties of the hospital staff in the decentralized model

S. #	Hospital Staff (Clinical)	Roles and Responsibilities
1	Chest Specialist	- Clinical Assessment - Counselling - Management of DR-TB patients as per guidelines - Monitoring of Adverse drug effects and reporting of Active TB drug-safety monitoring and management (aDSM) - Consultation with Provincial Review Panel team regarding difficult cases - Supervision of Paramedic and DR-TB staff (provided by Program) - Ensure complete recording and reporting as per protocol - Liaison with District Health Authority - Timely reporting of data to Program and District Health Authority
2	Pathologist	- Administrative role in the lab - Supervision of all testing related to DR-TB patients - Ensuring un-interrupted Microscopy, Gene Xpert testing and all other relevant tests on baseline and follow ups
3	Paramedic staff	Facilitation of patient within the hospital for - Sputum tests - Blood tests - Chest X-ray and ECG - Submission of samples to the lab - Receiving reports from the lab

4	Laboratory Technician	- Performing lab tests on baseline and follow ups - Microscopy, Gene Xpert, Blood tests
Hospital Administration		
5	Medical Superintendent	- Provision of space and furniture for OPD - Provision of space and furniture for waiting area - To ensure Nomination & availability of clinical and lab staff for DR-TB management - Provision of free of cost diagnostic and treatment facilities for DR-TB patients - Ensuring uninterrupted services to DR-TB patients in collaboration with Program - Ensuring storage of Second Line Drugs at hospital pharmacy - Hold Monthly meetings with Chest Specialist for updates on DR-TB management
Staff Proposed by the Program for Decentralized DR-TB Sites (Proposed by Punjab)		
6	DR-TB DOTS Facilitator (DOTS Facilitator / Paramedic)	- Development of monthly follow up lists - Management of patient files - Ensuring all required baseline and follow up tests are performed as per guidelines - Ensuring provision of Social Support as per protocol and monthly reporting of Social Support lists to Program - Provision of Second Line drugs to patients from the Pharmacy and limiting - patient's within hospital movement - Share monthly Medicine (Second Line Drugs) stock report and share with District and Provincial Authorities - Make Quarterly medicine demand and share with the Program and District administration - Entry of patient line lists in the ENRS (E-reporting) - Completeness of R&R Tools and timely reporting of Monthly, Quarterly and annual reports
7	DR-TB Field Staff (DOTS Facilitator / Paramedic)	Ensuring Contact Screening of DR-TB patients - Home Assessment of DR-TB patients for adequate infection control Measures - Development of linkages with BMUs nearest to patient homes for DOT and other emergency conditions - Retrieval of Lost to follow up patients - Liaison with District administration for patient data reporting and retrieval - Medicine delivery in case of emergency conditions - Liaison with all Gene Xpert sites and District Lab Supervisor for RRD lists and to ensure enrollment of all diagnosed DR-TB patients
District Health Authority		
8	Chief Executive Officer	- Monthly meetings with DTC and DHQ staff regarding DR-TB activities in the DHQ - Facilitating the DTC for Monitoring and Evaluation - Issue directions to all facilities for effective referral - Issue directions to DHQ administration for fulfilling all requirements for DR-TB management - To facilitate the DTC & BMU staff in retrieval of Lost to follow up patients through outreach teams if required - Facilitate the DTC to rectify the identified issues - Overall supervision of DR-TB activities in the district

9	District TB Coordinator (District Health Authority monitoring staff)	- Monthly monitoring of Decentralized DR-TB Site - Ensuring management as per National Guidelines - Develop linkages with all BMUs in the district for enhanced referral and timely diagnosis of DR-TB patients - Develop linkages between Gene Xpert sites and Decentralized DR-TB Sites - To help the BMU staff in retrieval of Lost to follow up patients - Ensure that timelines of reporting are followed - Facilitation in contact screening of DR-TB patients - Reporting of any gaps identified during monitoring to the CEO & Program - Making effort to rectify all identified gaps at district level - Ensuring timely stock reporting to Program for un-interrupted services - Regular briefing of DR-TB activities to CEO and DHO (Preventive Services) - Regular Capacity building and sensitization of BMU staff on DR-TB care
Provincial TB Control Program		
10	Provincial Program Officers (Provincial level Monitoring staff (MBBS+MPH))	- The Provincial Program has included DR-TB in the monitoring check list of the PPOs. - PPOs will be trained on National DR-TB Guidelines - Monitoring will be done on Patient centered approach - All aspects of TB will be monitored with focus on Programmatic management - Reporting of identified issues and making efforts for their rectification in collaboration with the divisional, district and health facility administrations
11	Provincial MDR-TB Coordinator	- Monitoring / Review of clinical data of all DR-TB patients on monthly basis (desk monitoring) - Field monitoring on regular intervals (All aspects of TB will be monitored with focus on Programmatic management) - Lead role in Provincial Review Panel (Provision of clinical consultation for difficult to treat patients) - Consolidation of Rifampicin Resistant Detected (RRD) cases from all Gene Xpert sites in Punjab - Ensuring enrollment of all RRD cases - Develop linkages of decentralized sites with culture, LPA and DST laboratories - Consolidation of DR-TB data and reporting to NTP - Monthly and Quarterly analysis of DR-TB Data - Receive monthly Medicine (Second Line Drugs) stock report and coordinate provision of medicine to the health facility

The monthly follow up Cultures and LPA will be done at the Provincial Reference Labs and the culture labs established in different districts. The Drug Sensitivity and LPA will be supported through the National Reference Lab, however the Provinces are also in the process of upgrading their labs for provision of DST services. The follow up tests like sputum microscopy, blood tests and others (ECG, Chest X-rays) will be supported by the hospital.

Pre-Requisites for DR-TB Decentralization to DHQ hospitals:

1. Meetings with stake holders by the Provincial and National TB Control Program Teams
2. Site selection & identification by the DHQ Hospital administration and District Health Authority

3. Assessment of site by the DHQ Hospital administration and PTP/NTP Teams for the following:
   a. **Facility design:**
      - Space for OPD
      - Space for waiting area in line with infection control requirements
      - Adequate Medicine storage conditions (temperature and humidity monitoring)
   b. **Laboratory:**
      - Availability of Microscopy and trained staff
      - Availability of Gene Xpert Machine and trained lab staff
      - Equipped for routine lab tests (CBC, ESR, LFT, RFT, Electrolytes)
      - Equipped for other tests – ECG, Chest X-ray
   c. **Human Resource from Hospital:**
      - Availability & nomination of Chest Specialist (or Medical Specialist) from the health facility
      - Availability & nomination of Paramedic (specific for DR-TB) from the health facility
      - Cardiologist and Psychologist support (can be taken from medical specialist also)
   d. **Others:**
      - Availability of ancillary medicine for patients
      - Free of cost lab tests for DR-TB patients

4. Nomination of Technical Review Panel (bimonthly online meetings are advised to discuss difficult to manage cases)
5. Capacity building of staff responsible for DR-TB management

Technical Review Panel at PMDT central site, provincial and central levels

If any clinical or program related consultation is required by the team at decentralized site, the Program has also proposed a Technical Review Panel which will consist of the following members:

1. Clinical MDR-TB consultant from NTP
2. Provincial MDR-TB Coordinator
3. Relevant MDR-TB Physician from where the decentralization has occurred.
4. Chest specialist from the decentralized site

The Chest Specialist managing the DR-TB patients at the decentralized site will generate an email to the above mentioned pre-defined group of people and share all the patient reports and prescriptions. It will be responsibility of the Review Panel to discuss the case and reply with decision within 24 hours. The patient may also be referred to the Central PMDT Site for consultation if required.

Merits of Decentralization:

1. Availability of DR-TB services in the same district as the patient
2. Cost effective for Program
3. Cost effective for patients
4. Less travel fatigue for patients
5. Less travel expenditure for patients
6. Better infection control
7. Improved diagnosis due to enhanced sensitization of staff
8. Better side effects management
9. Improved treatment success rate through timely monitoring
10. Decreased Lost to follow up
11. Decreased early death rate

Section 3:

Case Finding Strategies and Mycobacteriology services for management of RR-MDR-TB

TB laboratory network and diagnostic services[2]

In Pakistan TB laboratory network is established to provide services for bacteriological diagnosis of TB in patients with signs and symptoms of tuberculosis, testing for rifampicin resistance (RR) before start of TB treatment, comprehensive drug susceptibility testing for RR patient to detect resistance to guide effective treatment regimen and culture services for monitoring treatment response. Pakistan TB laboratory network is comprised of microscopy, GeneXpert, culture and DST laboratories (Table 6).

Table 6 TB laboratory network and diagnostic services in 2019

	Total TBMU	Microscopy*	GeneXpert**	Culture	DST	
					gDST (LPA)	pDST (MGIT)
Pakistan	**1536**	**1536**	**327**	**10**	**10**	**6**
Punjab	654	654	131	5	3	2
Sindh	432	432	94	5	3	1
Khyber Pakhtunkhwa	217	217	37	2	2	1
Balochistan	111	111	31		1	1
FATA	22	22	6			
Gilgit Baltistan	30	30	12	1		
Azad Jammu Kashmir	59	59	10	1		
ICT	11	7	6		1	1

*Source: *Respective Provincial TB programs, 350 private laboratories engaged in PPM-1 not shown ** 378 in August 2020 (gDST=genotypic DST, pDST=phenotypic DST)*

National Strategy for RR/MDR case finding

National guideline recommends that all TB patients should be screened for RR at time of enrollment on TB treatment, which is important to ensure correct treatment (Figure 8).

Diagnostic tool for detection of rifampicin resistance

The Xpert MTB/RIF is the only WHO-recommended rapid molecular diagnostic test that simultaneously detects TB *(M. Tuberculosis)* and resistance to rifampicin within two hours. Other diagnostic tool like Line probe assay (LPA) and liquid DST can detect rifampicin resistance but Xpert has advantage over these test:

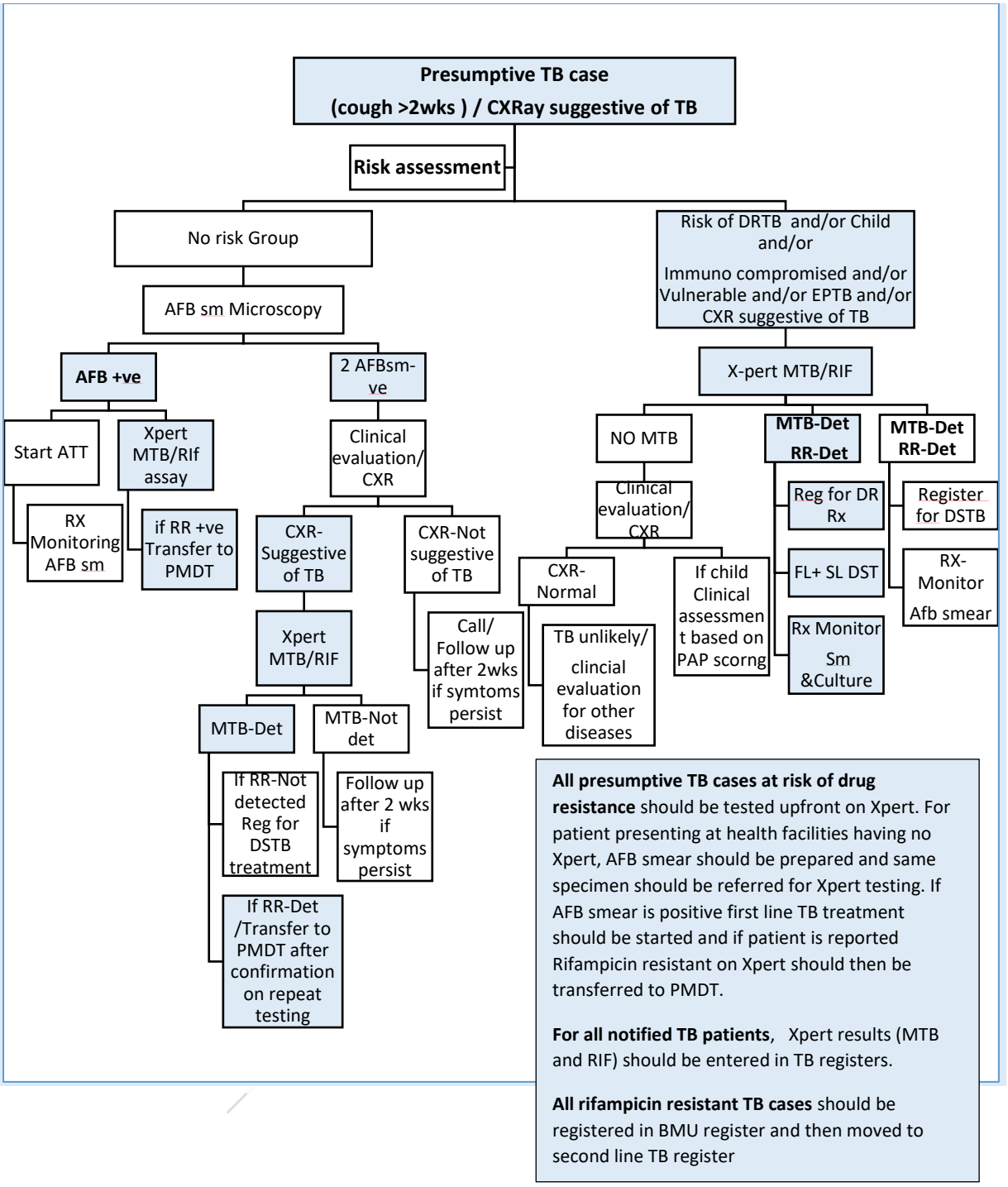
- Xpert can be performed in decentralized laboratories as infrastructure requirement are low
- Results are available within two hours
- Staff can perform test with minimal amount of training

Recommendation for Xpert testing:

WHO recommends use of **X-pert MTB/RIF** as an initial diagnostic test for TB in all individuals. **Smear microscopy** is an accessible test to diagnose the most infectious TB patients, but it is less sensitive than Xpert, and cannot diagnose RR. Although Xpert coverage has improved significantly In Pakistan, AFB microscopy is available in all TBMUs, while only 25% (378) of the TBMU are equipped with Xpert facilities. High volume centers were selected for Xpert and these health facilities with Xpert contribute to >50% of national TB notification. However an effective referral and

[2] NRL Annual Report 2019

Figure 8 Algorithm for diagnosis of tuberculosis and Rifampicin resistance



transportation system from TBMUs to Xpert laboratories is also required to ensure equal access and universal testing. The plan is to implement specimen referral and transport system from BHU/RHC to BMU and from BMU to Xpert site.

National guideline recommends to ensure testing of the following group of patients, while the test is not yet accessible at all sites and for all patients with presumptive TB. In view of limited resources, onsite availability of AFB microscopy and Xpert, and risk assessment, National guideline recommends that:

- All presumptive TB patients at higher risk of having RR-TB e.g. those who have history of anti TB treatment or contacts to known RR-TB patients should be tested upfront on Xpert for diagnosis of TB and drug resistance.

- All presumptive TB cases who are likely to have paucibacillary TB disease (few bacilli) e.g. immune-compromised (HIV) , children below 15 years and patients with extra pulmonary TB should be tested with Xpert for diagnosis of TB as it more sensitive in diagnosis of TB compared with microscopy
- In settings where only AFB microscopy is available on site, Xpert should also be done for
    - All AFB smear positive TB patients at time of treatment initiation, because they are most infectious.
    - All AFB smear negative with chest x-ray findings suggestive of TB
- All health care workers having signs and symptoms of TB.

Active case finding of RR-TB among contacts of RR-TB patients

Most RR patients are detected because they go to the health services with symptom, so-called passive case finding. In addition active case finding for diagnosis of RR-TB is recommended among contacts of RR/MDR patients.

All household contacts should be reached, verbally screened and all with symptoms should be investigated using upfront Xpert. The PMDT treatment sites should ensure that DR TB close contacts are screened preferably within one week of patient enrollment. The treatment coordinator should visit the patient's home to perform contact screening, all contacts should be verbally screened using a pre-defined simple questionnaire and sputum samples from contacts with TB symptoms should be collected (following all SOPs of Infection Prevention & Control) and transported to the nearest Xpert facility for testing. Those contacts who are unable to produce sputum are guided to visit the nearest health facility or PMDT Site where further screening is done by the medical officer.

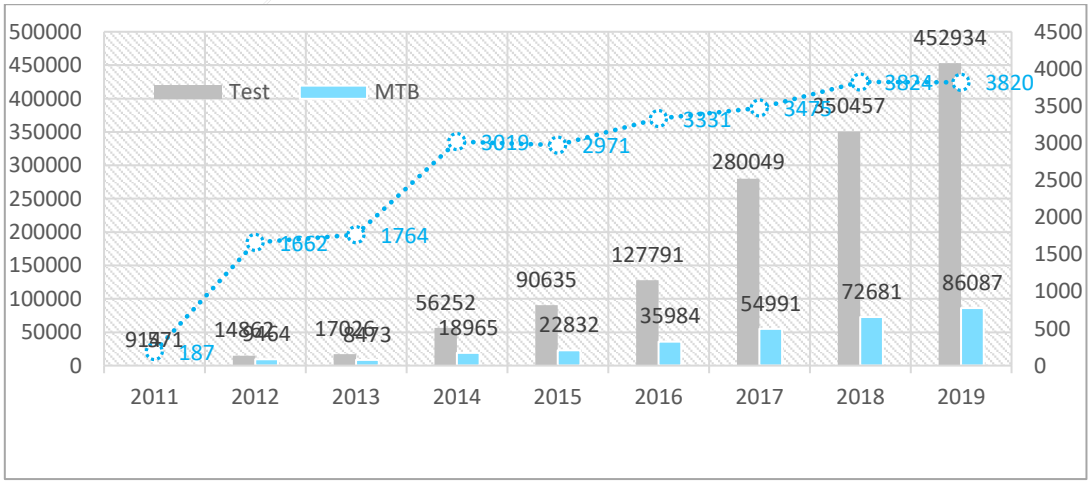
For details regarding preventive therapy of DR-TB contacts, refer to National guideline on Preventive treatment 2020.

Active case finding with Xpert testing is also done as mass screening in groups with increased risk of TB, usually in combination with chest x-ray, usually focusing on detecting TB, not especially DR-TB. The Indus Health Network has been doing screening camps in urban TB high prevalence areas in Karachi.

Scale up of Xpert and progress in Universal Rifampicin testing

Xpert Testing: In the year 2019, altogether 452,934 Xpert tests were performed. Including 299,229 collectively by NTP site, 138,730 by the TIH and 14,975 by MC supported sites. Among all tested 86, 0878 were reported positive for MTB and 3,820 rifampicin resistant cases were detected. The trend in testing is shown in figure 9.

Figure 9 Trend in Xpert testing, MTB confirmed TB cases and RR TB cases detected 2011-2019



Universal rifampicin testing: in 2019, among notified TB cases, 59% of **new bacteriologically confirmed PTB** and 89% among previously treated TB cases were screened for Rifampicin resistance.

More complete coverage of universal testing among previously treated TB cases is due to recommended Xpert testing for this group of patients from outset because of associated high risk of drug resistance.

Challenges in RR-TB diagnosis:

According to WHO estimates there are 28000 RR/MDR-TB cases among incident cases. The key challenges in case finding of RR-TB are:

- only 62% of the incident cases are notified and 1/3rd of TB cases are missed annually,
- among all notified only 38% are bacteriologically confirmed (48% among PTB) ,
- among bacteriologically confirmed incident cases only 59% were screened for RR.

Surveillance for rifampicin resistance:

With increasing availability of Xpert in all districts and national policy for universal rifampicin testing, monitoring of prevalence of RR by districts is now possible and recommended.

Data source for this surveillance activity is the district /facility (BHU/BMU) TB register. It is therefore important that all Laboratory results including AFB microscopy and Xpert results are entered systematically into the TB register. It is important that all RR cases detected are first registered in the facility (BMU/BHU) TB register regardless of where patient is registered for DRTB treatment. It is the responsibility of health facility staff to ensure that data entry is complete and registers are complete to allow monitoring of the proportion with bacteriological confirmation (B+TB) and with rifampicin resistance. It is also important that PMDT treatment coordinator communicates with health facility staff to confirm that the RR patient is also registered in the facility (BHU/BMU) register, helps in contact tracing and is provided with DOT and follow-up.

The following parameters should be monitored stratified by new and previously treated TB patients

1	**Percentage of Bacteriologically confirmed (B+ve) (by smear and/or Xpert) TB patient with a valid Rifampicin resistance result (expressed in %)**	
	Numerator	Number of Bacteriologically confirmed TB cases with valid result for rifampicin (Detected /not detected)
	Denominator	Number of Bacteriologically confirmed TB cases including AFB smear +ve and/or MTB+ve on Xpert
2.	**Percentage of Bacteriologically confirmed TB patients with Rifampicin resistance (expressed in %)**	
	Numerator	Number of Bacteriologically confirmed TB reported rifampicin resistant
	Denominator	Number of Bacteriologically confirmed TB cases with valid result for rifampicin (Detected /not detected)

Monitoring by facility and district will help the program to identify districts with unexpectedly low or high rate of TB, proportion of patients tested with Xpert and RR-TB and need to focus on any district /health facility for improving testing or diagnose RR cases. A trend over time will help to evaluate TB program performance.

Mycobacteriology services for management of the RR/MDR-TB

Mycobacteriology services are required starting from detection of rifampicin resistance (RR) TB, selection of treatment regimen, monitoring of treatment response, emergence of drug resistance, and treatment outcome is finally declared. Quality assured laboratory services play an important role in the management of MDR-TB. In this section we will briefly discuss about DST methods available in Pakistan and laboratory services for monitoring treatment response for RR/MDR patient on treatment.

Drug susceptibility testing (DST):

Initially DST was performed on LJ media (2009-2014), in 2015 DST was switched to MGT 960 media across all TB laboratory network. In 2017 second line LPA was introduced and is now available in all provinces.

As a newly diagnosed RR-TB patient presents in the PMDT site, a fresh sample is collected from all RR/MDR patients at the time of enrolment, which is transported to culture and DST laboratory for DST. A

comprehensive DST is performed on all samples using following methods **See Table below for drug tested and turnaround time for DST methods used**

- **Line probe assay: This is a Genotypic DST method,** MTB (*Mycobacterium Tuberculosis*) present in clinical specimens or in culture isolates are examined for presence of well-known resistance conferring mutations for each drug. All samples received in DST laboratory are processed for LPA
- **Phenotypic DST**: In this method the organisms are first grown in culture media (L J solid media and/or liquid media in MGIT). The organisms grown are then identified to confirm *MTB.*
  Next DST is performed by *growing MTB in media containing anti TB drugs at recommended critical concentration for each drug. The organism is reported resistant if it grows in presence of the drug and sensitive if its growth is inhibited in presence of a drug at the recommended critical concentration. Since 2015 automated liquid DST method are used for DST (MGIT 960).*

Table 7 Phenotypic DST: Critical Concentration of drugs for phenotypic DST on MGIT-960

FIRST LINE DRUGS (FLD)							
Drug	RMP	INH	ETH	STREP	PZA		
Conc(ug/ml)	1.0	0.1	5.0	1.0	100		
SECOND LINE DRUGS (SLD)							
Drug	LFX	MFX*	AMK	BDQ**	CFZ**	LNZ**	DLM**
Conc (ug/ml)	1.0	1.0	1.0				

*clinical breakpoint ** currently facility available in NRL

DST for new and repurpose drugs:

Monitor for emergence of resistance to these drugs is very important However DST capacity for Bedaquiline, Clofazimine, Linezolid and Delamanid is currently limited to National reference laboratory. While capacity building will take place in due course of time with wider availability of pure drugs, control strains and EQA program covering new drugs.

Due to current limited capacity it will not be possible to perform DST for these drugs for all patients at baseline. However, DST is recommended for patient who fail to convert at three month or culture reversion is reported after initial conversion.

Reporting of DST results:

Reporting of DST result depend on bacillary load of specimen and method used for DST.

A) Bacillary load in clinical specimen: Currently approximately 20% of the samples received in the laboratory from RR/MDR patients for DST are either smear negative or have scanty number of bacilli.

If clinical specimen are highly bacillary load (smear positive), reporting of DST results are high as

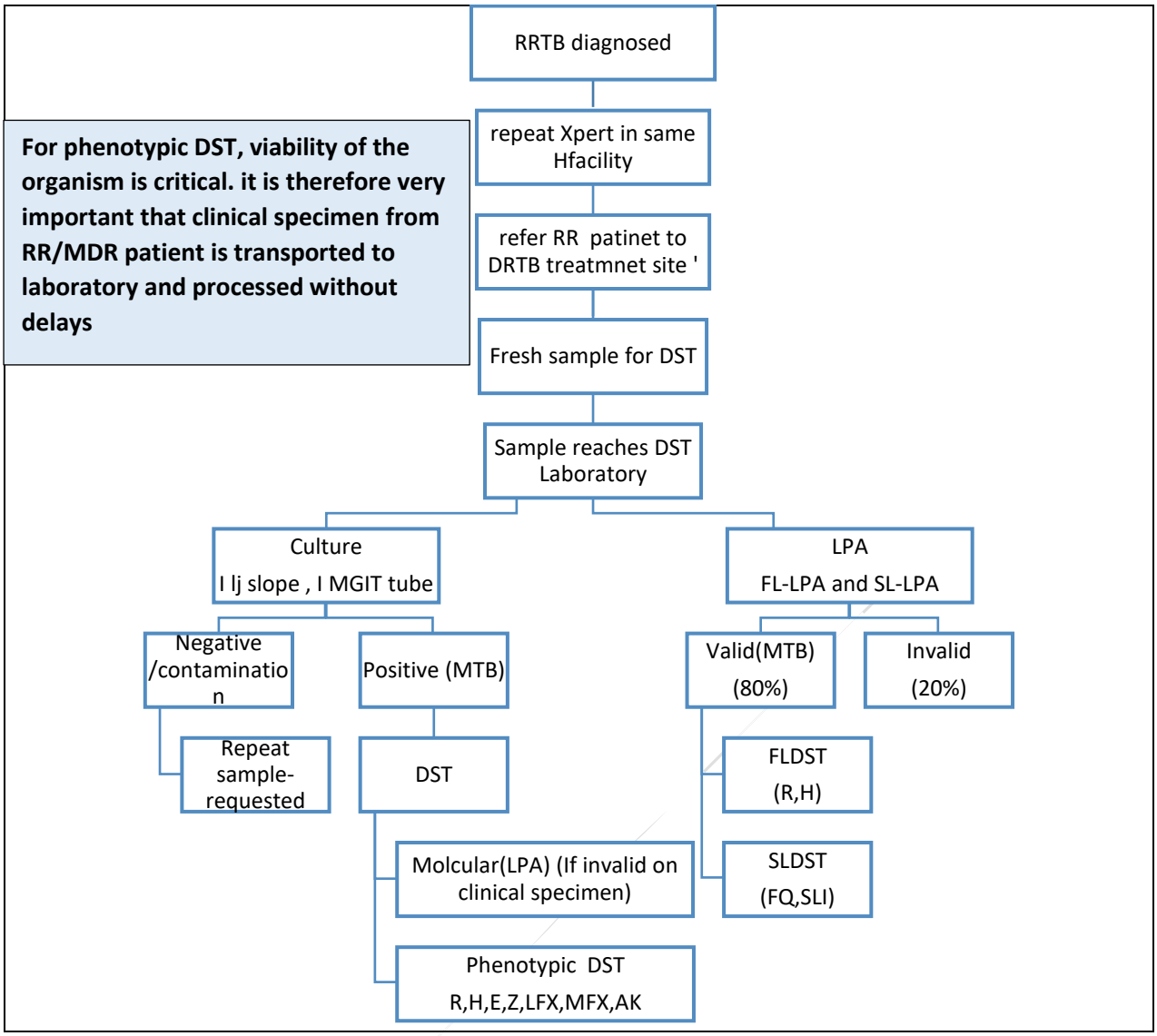
- Likelihood of valid results for rapid DST are high for direct samples with high bacillary load
- Likelihood of organism growing in culture media even if there are some delays in transportation. Phenotypic DST results will thus be available for drugs not tested on LPA.
- Culture isolates can be preserved and tested for DST for new drugs if indicated later during the course of treatment

If clinical specimens are scanty positive or negative for AFB smear likelihood of getting

- Rapid LPA results (within ten days) are low as only a fraction of clinical sample have Valid LPA results on direct samples
- Specimen transport time and condition are critical for these samples and likelihood of organism growing in culture media decreases with increase in time lapse from specimen collection

Possibility of these patient getting DST results decreases both for direct LPA and indirect DST (Figure 10).

Figure 10: Flow of specimen and Protocol for DST in TB laboratory



B) Use of clinical specimen or culture isolates for DST?

Direct DST is when clinical specimen is used directly for identification of resistance to a particular drug/drugs. The method has advantage that reports are available in short time. In routine clinical specimen are used for molecular DST methods (LPA)

Direct DST testing on clinical specimen using LPA is successful for >95% of AFB smear positive cases but only for 70% of samples with scanty bacilli and in 20-30% of all samples which are negative on smear and MTB is detected with Rif resistance on Xpert only

Indirect DST method is when the organism is first grown on culture media and then phenotypic or genotypic method are used for determining drug resistance. Turnaround time for DST time would be longer.

Table 8 Molecular and culture based phenotypic methods for DST.

	Method for DST	Commercial Name	Drugs tested	Type of DST	Turnaround Time (TAT)
1	**Molecular DST**				
	First line- LPA	MTBDR*plus*	R,H,	Direct	2 -10 days
				Indirect	Time to culture +2-5 days
	Second line-LPA	MTBDR*sl*	FQ, SLI	Direct	2 -10 days
				Indirect	Time to culture +2-5 days
2	**Phenotypic DST**				
	a. Liquid DST	MGIT960	R,H,E,Z,S, LFX,MFX, Am ?? Bdq*,CFZ*,DLM*,LNZ*	Indirect	24-30 days
	b. Solid DST**	NA	R,H,E,Z,S, LFX,MFX, Am	Indirect	60-90 days
	*DST for new drugs and repurposed drugs is currently only performed at NRL				
	** DST on solid media is currently not performed for routine DST services				

Interpretation of genotypic DST results:

When genotypic DST is performed using LPA, following terms are used (table 9):

"**Resistance detected**" is used when one or more "MUT probes" identifying specific mutations conferring resistance to the drugs are developed and in the absence of corresponding "WT probes" (resistance detected) or also WT probes are developed (hetero-resistance).

"**Resistance inferred**" is used when one or more WT probes in regions of the gene known to confer resistance to the drug are not developed, but MUT probes in the corresponding region are not developed. In this case the precise mutation cannot be reported, only the region where the mutation lies is identified. See Annex 4 Resistance conferring mutation and interpretations.

High and low level resistance: For FQ and INH, High level mutations are associated with high-level increase in MIC. Mutations associated with at least low-level increase in MIC are called low level resistance.

Correlation between phenotypic and genotypic DST resistance:

100% agreement of DST results between two DST is not seen for any of the drugs. MGIT DST once considered as "Gold-standard" is not perfect nor is the LPA or GeneXpert. Correlation between LPA and MGIT DST results is shown in table 10 (discordant results are shown in blue cells)

Table 9 Interpretation of LPA results: Resistance detected, inferred and hetero-resistance (WT= wild type, MUT=mutation)

Case	Result/Inter-pretation	WT reaction zones	MUT reaction zones	Descriptions /examples
1	**Resistance not detected**	**All WT probes are developed**	**No MUT probes are developed**	Depending on the specific drug – Resistance not detected
2	**Resistance detected**	One or more WT probes are not developed	One or more MUT probes in the corresponding region are developed	Depending on the specific drug: **Rifampicin and SLI** – Resistance detected **INH and FQ:** Depending on the mutation -Mutations associated with high-level increase in MIC detected; -Mutations associated with at least low-level increase in MIC detected
3	**Resistance inferred**	One or more WT probes	No MUT probes	Depending on the specific drug: **Rifampicin and SLI**

		are not developed	developed	– Resistance inferred **INH and FQ:** Depending on the mutation -Mutations associated with high-level increase in MIC inferred. -Mutations associated with at least low-level increase in MIC inferred.
4	**Hetero-resistance** (mixed infection of drug-susceptible and -resistant bacteria)	All WT probes are developed	Some MUT probes in the corresponding regions are developed	

Basic understanding and limitation of each DST method can help understand discordance.

- In genotypic DST, limited genes and sites are targeted, therefore resistance caused by mutations other than target sites are missed by genotypic DST
- Resistance caused by mutations resulting in elevated MICs but sensitive at critical concentration (e.g., Leu511Pro in rpoB) are missed on phenotypic DST

In Pakistan, among rifampicin resistant cases detected on Xpert, almost 13% are missed on MGIT-DST (RR/MDR patient on second line drugs are reported as rifampicin sensitive) whereas INH resistance is missed more on LPA: only 85% are detected on LPA. A significant number of patients reported as INH sensitive initially are later reported INH resistant on MGIT –DST). Similarly about 10% of Fluoroquinolone resistance is missed on LPA. Emerging resistance (mixed populations) may also be missed due to limit of detection.

Table 10 Correlation between phenotypic and genotypic DST results in DST performed in NRL 2019

	Genotypic DST results	Phenotypic DST results			Genotypic DST performance			
		Resistant	Sensitive	Total	Sensitivity	Specificity	PPV	NPV
Rifampicin	Resistant	775	159	934	97.5%	86.9%	83.0%	98.1%
	Sensitive	20	1055	1075				
	Total	795	1214	2009				
Isoniazid	Resistant	838	5	843	85.2%	99.5%	99.4%	87.5%
	Sensitive	146	1020	1166				
	Total	984	1025	2009				
Fluoroquinolone (Levofloxacin)	Resistant	394	41	435	91.6%	94.0%	90.6%	94.7%
	Sensitive	36	639	675				
	Total	430	680	1110				
Second line injectable	Resistant	23	4	27	82.1%	99.6%	85.2%	99.5%
	Sensitive	5	1071	1076				
	Total	28	1075	1103				

PPV= Positive predictive value, NPV: Negative predictive value

Clinical implication of resistance missed on rapid DST (LPA) are more serious than those missed on phenotypic DST as decisions regarding treatment regimen are taken on Genotypic DST and 4-8 week on treatment have already passed by the time phenotypic DST is available.

Human or laboratory error can result in discordance or erroneous results and test should be repeated if there is a reason to doubt the results. However, as a general principle for clinical management "**Resistance results overrides susceptible results by any DST methods for any drug"**

Monitoring Treatment response of RR/MDR patients on second line treatment:

Smear microscopy is available in all TBMU and DRTB treatment sites. Smear should be done at time of enrolment on second line treatment to assess bacillary load, guide contact tracing and infection control and as baseline for comparison of smear results performed during course of treatment at each follow up visit. Smear result are rapidly available for assessment of treatment response. It is therefore important to ensure QC and EQA for smear microscopy in these facilities.

TB culture: For monitoring treatment response, in addition to DST laboratories, culture laboratories (only) are established to share the bulk of cultures load required for monthly monitoring of treatment response during monthly follow up visits. These culture (only) laboratories only have facilities for solid culture (LJ media) whereas automated liquid culture (MGIT) facilities are available in laboratories doing DST.

Table 11 Culture reporting time

	Availability of Culture facilities	Protocol for culture	Reporting time if culture is positive	Reporting time if culture is negative*
1	MGIT+ LJ	I tube MGIT and I slope LJ	2 to 9 wks	9Wks
2	LJ only	2 slopes LJ	3 to 9wks	9Wks

*culture is incubated for maximum of six weeks in MGIT and 9 weeks for LJ.

The monitoring schedule for follow-up including smear microscopy and culture are found in Section 4 Treatment regimens, tables 21 for STR and 24 for LTR.

Operational Guide for managing Laboratory services for RR/MDR patients

In the section below there is a quick checklist of "To do things "with regard to laboratory services, step by step starting from the time when the patient reports for the very first time to DRTB treatment site and when he comes for monthly follow up what investigation are needed and when additional DST is recommended during the course of treatment

Step-1: TBMU - when patient is reported Rifampicin resistance

It is recommended that all those who are reported with Rifampicin resistance in the absence of any known risk for drug resistance (previous treatment or contact with DRTB patients), Xpert testing should be repeated (clearly mention in request form that test is being repeated for confirmation of RR) in same health facility before referring patient to specialized DRTB treatment.

Ensure that:

- Xpert is repeated for all patient not known to be at risk of drug resistance
- RR-TB Patient is registered in TBMU-register before referring to DRTB treatment site –and then is transferred out to DRTB treatment site
- RR-TB Patient is referred with completed referral form
- RR-TB patient is enrolled and DR-TB treatment is initiated as early as possible.
- Actively follow up patient status from respective DRTB treatment site and enter DRTB registration number in TB register.

Step 2:-PMDT - When patients report to PMDT treatment site for the first Time

Check GeneXpert test reports

- Interview patient for risk assessment –ask previous history of TB treatment and any contact with known DRTB or TB patient?
- In case no risk is identified, check for repeat test report
- If there is no evidence of repeat testing – repeat GeneXpert test at DRTB treatment facility and clearly mention in request form that test is being repeated for confirmation of RR
- Explain to patient and guide to submit fresh sample for repeat test at Xpert lab in the DRTB treatment site.

Ensure good quality samples are collected for DST

The clinical sample collected for DST at the time of registration is the most important and is basis of selection/modification of treatment regimen. For reliable results, ensure that

- Good quality and appropriate quantity of sputum sample is collected
- Sample is transported at earliest so that sample reaches the laboratory within 72 hours of collection.

The chances of getting a valid DST results decreases as time increases between sample collection and specimen processing in the laboratory. Key points to remember to ensure a valid DST results are available for each of the registered patients are listed below

Table 12 Quick checklist for DST request

• **Explain to patients why sputum examination is important**
• Instruct patients on collection of good quality specimen
• Ensure that optimally two specimens are collected from each patients
• Ensure that specimen are packed properly to avoid leakages during transportation
• Ensure that specimen are safely kept in cold place (refrigerator/coolbox)till it is picked up by courier for transportation.(avoid exposure to sunlight)
• Ensure standard request form is used and clinical information is complete on request form
• Ensure specimen transport in cold chain
• Ensure specimen reaches laboratory within 72 hours of collection for optimal results
• Avoid specimen pickup on Saturdays /Fridays (or day preceding public holidays).

To avoid delays in specimen transport, patient follow up visits should not be organized on weekends and days preceding public holidays. These steps will reduce risk of contamination or invalid results.

Step-3: When patients report to DR-TB treatment site for follow-up:

RR/MDR patients on second line treatment need stringent follow up for monitoring of adverse reactions as well as for response to treatment. Table summarizes the DST and culture schedule for patient on short course and long course treatment for RR/MDR.

Table 13 Key point to remember during Patient follow up visit

a)	AFB smear and culture are recommended every month during each follow up visit
b)	AFB smear and culture are the only two methods recommended for monitoring treatment response, Xpert MTB/RIF assay is not recommended for monitoring treatment response
c)	AFB smear should be done in local laboratory for rapid results – collect two samples and send one to local lab for AFB smear
d)	Good quality of specimen is even more critical for culture during follow up
e)	Specimen should be transported to the laboratory at earliest (should reach laboratory within 72 hours)
f)	Delay in specimen transportation may results in i)failure of small number of bacilli to grow on culture or ii) other organism to over grow resulting in contamination
g)	With improvement in clinical condition patient may encounter difficulty in expectorating sputum or may show reluctance to expectorate. In such condition, counselling of patient and effort to make him/her understand the importance of sputum examination can help.

Importance of clinical and laboratory coordination and communication:

Both clinical and laboratory staff are involved in TB care of the patient It is therefore important that staff at clinical and laboratory end communicate with each other **for managing RR/MDR TB patients**

Table 14 Key consideration for effective laboratory services

1. Relevant PMDT site is fully aware of the linked laboratory for culture and DST services and availability of culture and DST method in each
2. For effective Communication between laboratory and clinical staff a Point of contact is identified both at the PMDT treatment site and culture and DST Laboratory who shall respond to issues related to DR-TB by phone or email for example lack of clinical information on request form, leakage of specimen, request for repeat specimen in case of contamination etc. Similarly PMDT staff may call/Email laboratory staff regarding reporting delays, discuss discordant results and request for DST on follow positive culture.
3. A good referral and transport mechanism is established between i) treatment sites and culture/ DST laboratories. Ii) Between Culture and DST laboratories (if different) so that any follow culture which need DST is immediately transferred from culture to DST laboratories.
4. All culture isolates specially the baseline and month ¾(if patient remains positive) or any positive culture after initial conversion are preserved in the laboratory
5. Complete clinical information is provided on request form (NIC and ENRS) so that all isolates are linked to individual patient.

See also annex 6 Recording and reporting of laboratory results from facilities with or without Xpert.

Step-4: When patient fails to convert by three month or culture reversion is reported

Starting from 2020 al RR/MDR patients are now initiated on second line drug regimen containing bedaquiline, linezolid, clofazamine and delamanid. DST for these drugs are not performed currently in routine, however it is important that DST is performed on culture isolates from all patient who fail to convert by month three. DST should be performed on culture isolates at baseline and during follow to distinguish between initial and acquired drug resistance. AS currently there is only one laboratory necessary arrangement will be required for testing

Table 15 Recommendation for surveillance of emerging drug resistance:

	Recommendation	Responsibility
1.	Furnish complete clinical information on laboratory request form (see Section 12 M&E) Patient CNIC, Registration no. Data of registration and treatment regimen Eg . STR / LTR including BDQ ,CFZ, MFX, LNZ	Treatment site
2.	Preserve all positive cultures (baseline and follow up cultures)	Culture /DST lab
3.	If patient fails to convert by three month, baseline culture and follow up culture need to be tested for BDQ,CFZ,LNZ	NRL
4.	If NRL is providing both culture and DST services to PMDT sites – follow up with NRL on Email and provide missing information if any	NRL/PMDT site
5.	If NRL is providing DST services to PMDT and culture services are provided by another Laboratory – PMDT site to coordinate with both laboratories and culture laboratory need to send follow up culture to NRL for DST	PMDT/NRL/Culture laboratory
6.	If both culture and DST services are provided by a laboratory other than NRL , PMDT site to coordinate with respective DST laboratory , DST laboratory to send both baseline and follow up culture (3 or4M) isolates to NRL	PMDT/PRL
7.	If DST and culture laboratory are different. PMDT site to coordinate with both. Culture laboratory to send follow up culture to DST laboratory and DST laboratory to send baseline and follow up culture to NRL	PMDT/PRL/Culture laboratory

Section 4:

Treatment of DR-TB

Background

From the beginning of PMDT in 2010, two-year long treatment regimens **(LTR)** were used for RRR/MDR-TB. From 2018 the shorter treatment regimen **(STR)** lasting 9-11 months gradually replaced the LTR in patients without Fq-resistance. All oral LTR was initiated in July 2019 following WHO recommendations. From February 2020 the injectable drug in STR was replaced by Bdq in line with new WHO guidelines 2019 and June 2020.

The treatment success rate declined as the case number increased to just above 60%, with deaths and LTFU main reasons for "unsuccessful" treatment. There seemed to be some improvement 2017 and 2018 (table 16).

Table 16 Result of all DR-TB treatment: all country. All Pakistan (2015-2017: MDR/XDR/RR-TB)

Year	N	Cured	Complete	Died	Failed	Lost to Follow-up	Not Evaluated	Still under Tx	Grand Total	Success
2008	1	100,0 %	0,0 %	0,0 %	0,0 %	0,0 %	0,0 %	0,0 %	100,0 %	100 %
2009	25	96,0 %	4,0 %	0,0 %	0,0 %	0,0 %	0,0 %	0,0 %	100,0 %	100 %
2010	209	69,4 %	2,9 %	14,8 %	3,3 %	8,6 %	1,0 %	0,0 %	100,0 %	72 %
2011	499	72,1 %	4,4 %	12,8 %	4,8 %	5,2 %	0,6 %	0,0 %	100,0 %	77 %
2012	889	70,4 %	4,4 %	13,7 %	4,6 %	4,3 %	2,6 %	0,0 %	100,0 %	75 %
2013	1570	69,6 %	1,7 %	17,4 %	4,0 %	5,4 %	1,8 %	0,0 %	100,0 %	71 %
2014	2662	64,9 %	1,6 %	17,2 %	3,5 %	9,7 %	3,1 %	0,0 %	100,0 %	66 %
2015	2621	60,4%	4,6%	19,0%	4,6%	10,6%	0,8%	0,0%	100,0 %	65%
2016	2881	61,1%	3,5%	18,0%	4,7%	9,6%	3,0%	0,0%	100,0 %	65%
2017	3081	61,5%	1,5%	19%	4%	10%	4%			63%
2018**	1565	60,6	4,8	15,2	4,7	10,1	2,8	1,6	100,0%	65,4

** 1+2 quarter 2018 (from NTP Annual report 2019 table 18)

Among RR patients enrolled the first half of 2018 treatment success was 65%. When assessed by regimen and resistance to FQ, patients on STR (with injection, mainly FQ-S) had the highest success rate (72%), but with high LTFU and death, indicating that shortening the regimen improved outcome but did not prevent deaths and LTFU. Decentralization should improve outcomes. LTR FQ-S with comparable patients as STR, had slightly lower success rate (68%), higher failure rate (5%). LTR FQ-R had lower success rate (60%), high death rate and very high failure (11%). LTR FQ-UK had the lowest success rate (57%), with high death rate, LTFU, suggesting that not having test for FQ-resistance (LPA) may be proxy for other unfavorable factors, including limited access (table 17).

Table 17 Treatment outcome 2018 by regimen (STR, LTR) and FQ-resistance (sensitive, resistant, unknown)

Regimen	**No. of Patient put on Treatment**	**Cured**	**Completed**	**Failed**	**Died**	**Lost to Follow-up**	**Not Evaluated**	**Still Under Treatment**	**Success Rate**
STR	329	70 %	2 %	1 %	11 %	13 %	3 %	0 %	72 %
LTR FQ-R	378	57 %	3 %	11 %	18 %	5 %	3 %	3 %	60 %
LTR FQ-S	630	63 %	6 %	5 %	13 %	10 %	2 %	2 %	68 %
LTR FQ-UK	228	48 %	9 %	0 %	22 %	16 %	4 %	1 %	57 %
Total	1565	61 %	5 %	5 %	15 %	10 %	3 %	2 %	65 %

Groups of Anti-TB Ddrugs

WHO has entered TB medicines for DR-TB in **three groups** (A, B and C) in table 18. They are ranked based on the balance of effectiveness to safety. Choice should also be determined by: a preference for oral over injectable agents; the results of drug-susceptibility testing (DST); the reliability of existing DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug-drug interactions.

Table 18 Grouping of medicines recommended for DR-TB regimen

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

High-dose isoniazid can also be used in the regimens of adults and children with confirmed susceptibility to isoniazid, or in the presence of mutations that do not confer high-level resistance to isoniazid (i.e. isolated *inh*A mutations).

The drugs used in STR and LTR are listed in tables 19 (adults) and 20 (children).

Malabsorption of DRTB drugs

TB is one of the consequence which can occur as a result of malabsorption syndrome characterized by impaired absorption of nutrients, vitamins, minerals and drugs from GI tract. Due to reduced systemic absorption of DRTB drugs the required concentration is not reached upon in the blood and foci of infection further leading to ineffective treatment. In patients receiving optimal DRTB regimen (as per DST pattern) who still fails to improve clinically or radiologically, malabsorption syndrome must be suspected.

In view of above scenario and in severely ill patients with DRTB, ***parenteral therapy*** must be considered and preferred choice of therapy. There are many benefits of intravenous admission of anti-DRTB medications. Some are as follows:

- 100% bioavailability
- Achievement of rapid concentrations of drugs in bloodstream
- Less number of side effects
- Possibility to intensify treatment
- Less chance of treatment interruption
- Accurate dosing

Similarly, role of nutrition is also significant in such patients wherein correction of malnourished patients with provision of nutritional supplements may be considered.

Selection of Treatment Regimen

When the RR patient meets the clinician in the PMDT site, the clinician should clarify if the patient is eligible for STR. If that is the case, the clinician should explain well that STR has the major advantage of being shorter, with less work/cost for patient/family and health services. Treatment success is generally higher with STR because LTFU is lower. On the other side the number of tablets per day is larger in STR but the total number for whole treatment is less. Adverse events are frequent in both STR and LTR, but are usually manageable with close follow-up, information and management. Usually the patient starts STR if criteria are fulfilled and while waiting for result of LPA and DST for FQ resistance. If FQ resistance is found, the regimen will be changed to LTR.

Patients who are not starting STR, will start one of 3 LTR regimens:

- **LTR1** in patients who have not used SLDs before and if Fq sensitive or still unknown resistance result,
- **LTR2** if any FQ resistance,
- LTR3 in patients with (1) failure of STR or LTR, (2) relapse of STR or LTR or (3) resistance to FQ as well as Bdq/SLI (see table 22 with LTR regimens).

RR patients can also be treated with other short regimens in projects under strict operational research (OR) conditions (see section 15 Operational research). These regimens include **Modified STR all-oral regimens** (many using Lzd) and the **BPal regimen** using Bdq, Pretomanid and Lzd for 6 months in patients with Fq resistant strains. **Other OR options can also be explored as and when required.**

Short all-oral regimen:

Inclusion criteria for STR are:

- no previous treatment with second-line medicines used in the regimen for more than 1 month;
- no extensive TB disease as per WHO recommendations (bilateral cavitary disease, or Cavitary lesion (in aggregate) more than 4 cm, extensive parenchymal damage on chest radiography. The clinician should follow WHO recommendations and should not unnecessarily exclude patients from the STR because of unusually wide definition of extensive disease.
- extrapulmonary TB except military TB or TB meningitis; In children aged under 15 years, only lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) to be included;
- not pregnant;
- children 6 years old and above.
- no resistance or suspected ineffectiveness of a medicine in the shorter regimen (in practice only resistance to isoniazid with both *inhA* and *katG* mutations excludes);

Ideally resistance to Fq should be ruled out before starting STR, especially since almost half (35-40%) of RR patients have FQ resistance: The reasons for starting STR while waiting for LPA include the following:

- LPA results are often delayed
- Most patients do not accept postponement of treatment once they have come to a PMDT site, often quite far.
- Patients may live in crowded conditions, with small children in the household, with risk of continued transmission to vulnerable persons.
- Patients may have serious disease and treatment cannot wait.

STR regimen:

- This short standardized regimen is given for a total of 9-11 months, abbreviated as: 6 Bdq-Mfx/Lfx-Eto-Cfz-Z-H high-dose-E / 5 Mfx/Lfx-Cfz-Z-E.
- The intensive phase includes 6 months of Bedaquiline, Levofloxacin, Etionamide, Clofazimine, Pyrazinamide, high dose Isoniazid and Ethambutol.
- The continuation phase lasts a fixed 5 months with Levofloxacin, Clofazimine, Pyrazinamide, and Ethambutol.

- If smear is negative at month 6, end the intensive phase. If the smear is positive at month 6, treatment is classified as failure. If monthly cultures from 3 months onwards are positive, resistance to Fq and Bdq should be tested by LPA and DST and the regimen changed according to DST results.
- Etionamide and/or high dose isoniazid may be omitted after 4 months if there are adverse reactions in patients who have converted, and the STR regimen continue otherwise unchanged.
- For formulation and drug dosage, see table 19 for adults and table 20 for children. The dose must be adjusted to the weight at each follow-up visit.

Principles of treatment with STR:

- The treatment should be "person-centered", informing and counselling about the disease and treatment at start and when needed, agreeing with the patient the most practical way to directly observe the treatment (DOT) and regularly follow-up and provide support throughout the treatment period (see Section 5 education counselling and DOT).
- It is important to explain to the patient starting STR that the treatment may later be changed to LTR because of drug resistance, treatment failure, treatment interruption more than two months, intolerance, and other reasons.
- Patients should be carefully monitored with monthly smear and culture (two samples each time). If culture is positive at month 3 or later, it should be sent for LPA and DST to detect acquired resistance, especially to Fq and Bdq because there is concern of increased risk, especially in settings with high Fq resistance, as Pakistan. (see paragraph on monitoring later in this section)
- Vigilant monitoring with implementation of an effective aDSM component is needed to timely detect and manage adverse events. (See paragraph on monitoring later in section).

Table 19 Daily drug dosage by patient weight (adults) – STR and LTR

Drug	*Weight-based daily dose*	*Formulation*	*30-35kg*	*36-45kg*	*46-55kg*	*56-70kg*	*>70kg*	*Usual upper daily dose*
Drugs used in STR								
Bedaquiline		100 mg tab	4 tabs od first two weeks, then 2 tabs od M/W/F for 22 weeks					400 mg
Clofazimine		50 mg cps or tab	2	2	2	2	2	100 mg
		100 mg cps or tab	1	1	1	1	1	100 mg
Levofloxacin		250 mg tab	3	3	4	4	4	1.5 g
		500 mg tab	1.5	1.5	2	2	2	1.5 g
		750 mg tab	1	1	1.5	1.5	1.5	1.5 g
Moxifloxacin	Standard dose	(400 mg) tab	1	1	1	1	1	400 mg
	High dose	(400 mg) tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg
Ethambutol	15-25 mg/kg	400 mg tab	2	2	3	3	3	
Ethionamide or Prothionamide	15-20 mg/kg	250 mg tab)	2	2	3	3	4	1 g

Isoniazid	4-6 mg/kg (standard dose)	300 mg tab	2/3	1	1	1	1	100 mg tablet can facilitate administration of certain dosages
	10-15 mg (high dose)	300 mg tab	1.5	1.5	2	2	2	
Pyrazinamide	20-30 mg/kg	(400 mg) tab	3	4	4	4	5	
		(500 mg) tab	2	3	3	3	4	
Drugs only used in LTR								
Drug	*Weight-based daily dose*	*Formulation*	*30-35kg*	*36-45kg*	*46-55kg*	*56-70kg*	*>70kg*	*Usual upper daily dose*
Linezolid		600 mg tab	(<15 years)	(< 15 years)	1	1	1	1.2 g
Cycloserine or terzidone	10-15 mg/kg	250 mg cap	2	2	3	3	3	1 g
Delamanid		50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg
Imipenem-cilastatin		500 mg + 500 mg powder for injection, vial (10 ml)	2 vials (1g + 1 g) bd	To be used with clavulanic acid				
Meropenem		1 g powder for injection , vial (20 ml)	1 vial 3 times per day or 2 vials bd	To be used with clavulanic acid				
Clavulanic acid		125 mg clavulanic acid as amoxicillin/clavulanate, 500 mg/125 mg tab	1 bd	1 bd	1 bd	1 bd	1 bd	Only to be used with carbapenems
Amikacin	15-20 mg/kg	500 mg/2 mL solution for injection, ampoule	2.5 mL	3 mL	3-4 mL	4 mL	4 mL	1 g
Streptomycin	12-18 mg/kg	1 g powder for injection, vial	Calculate according to the dilution used	1 g				
P-aminosalicylic acid	8-12 g/day in 2-3 divided doses	PAS sodium salt (equivalent to 4 g PAS acid) sachet	1 bd	1 bd	1 bd	1 bd	1to 1.5 bd	12 g
		PAS acid (4g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd	

Notes, abbreviation: cap: capsule; g: gram; kg: kilogram; mL: milliliter; mg: milligram; M/W/F: Monday, Wednesday, Friday.

Clinicians may decide to exceed the "usual upper daily dose" in particular cases to improve therapeutic effect.

(Isoniazid) The higher dose may be used except when: there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has high-level drug resistance. Pyridoxin is given with Isoniazid in patients at risk (e.g. those with HIV or malnutrition).

(Amikacin, Streptomycin) The weight-based daily dose is for 6 or 7 days per week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

Amoxicillin/clavulanic acid is only recommended as a companion agent. Because of a lack of data from the latest analysis on longer MDR-TB regimens in adults, gatifloxacin, isoniazid and thioacetazone are not included in the grouping table of medicines used for longer regimens. Pretomanid is recommended to be used only as part of the package of the BPaL regimen.

(Clavulanic acid) Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed-dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

Table 20 Daily drug dosage by patient weight (children) – STR and LTR

Drug	*Weight-based daily dose*	*Formulation*	*5-6 kg*	*7-9kg*	*10-15kg*	*16-23 kg*	*24-30 kg*	*31-34 kg*	*>34 kg*	*Usual upper daily dose*	*Comments*
Drugs only used in STR											
Bedaquiline		100 mg tab	-	-	-	2 tabs od for 2 weeks; then1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks			Only in patients aged >5 years (lower dose from 15–29 kg; higher dose from >29 kg
		20 mg dt	-	-	-	10 dts od for 2 weeks; then 5 dts od M/W/F for 22 weeks		20 dts od for 2 weeks; then 10 dts od M/W/F for 22 weeks			
Clofazimine	2-5 mg/kg	50 mg cps or tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/kg/day is too high
		100 mg cps or tab	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
Levofloxacin	15-20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	
		250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g	
Moxifloxacin	10-15 mg/kg	100 mg dt	0.8	1.5	2	2	4	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in < 6 months
		400 mg tab	2 mL	3 mL	5 mL	0.5 or 0.75	1	(>14 y)	(>14 y)	400 mg	
Ethambutol	15-25 mg/kg	100 mg dt	1	2	3	4	-	-	(>14 y)		
		400 mg tab	3 mL	4 mL	6 mL	1	1 or 1.5	2	(>14 y)		
Ethionamide or Prothionamide	15-20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	44	(>14 y)	1 g	
		250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1g	

Isoniazid	10-15 mg (high dose)	50 mg/5 mL soln	2/3	1	1	1	1			100 mg tablet can facilitate administration of certain dosages	300 mg isoniazid tablet can be used in patients >20 kg.
		100 mg tab	1	1.5	2	3	4	4	(>14 y)		
Pyrazinamide	20-30 mg/kg	150 mg dt	1	2	3	4 or 5	-	-	(>14 y)		
		400 mg tab	0.5	0.75	1	1.5 or 2	2	2.5	(>14 y)		
		500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)		
Drugs only used in LTR											
Linezolid	15 mg/kg od in <16 kg	20 mg/mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	600 mg	
	10-12 mg/kg od in >15 kg	600 mg tab	0.25	0.25	0.25	0.5	0.5	0.5	0.75		
Cycloserine or terzidone	10-15 mg/kg	125 mg/ mini capsule (cycloserine)	2	2	3	3	3			1 g	
		250 mg cap	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
Delamanid		50 mg tab	-	-	-	-	1 bd	1 bd	2 bd	200 mg	Only in patients aged >2 years (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years).
Imipenem-cilastatin		500 mg + 500 mg powder for injection, vial (10 ml)									Not used in patients aged < 15 years (use meropenem)
Meropenem	20-40 mg/kg iv every 8	1 g powder for injection , vial (20 ml)	2 mL	4 mL	6 mL	8-9 mL	11 mL	(>14 y)	(>14 y)		To be used with clavulanic acid

	hours										
Clavulanic acid		62.5 mg clavulanic acid as amoxicillin/ clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 mL	2 mL bd	3 mL bd	5 mL bd	8 mL bd	10 mL bd	(>14 y)	(>14 y)		Only to be used with carbapenems
Amikacin	15-20 mg/kg	500 mg/2 mL solution for injection, ampoule	0.4 mL	0.6 mL	0.8-1.0 mL	1.2-1.5 mL	2.0 mL	(>14 y)	(>14 y)	1 g	
Streptomycin	20-40 mg/kg	1 g powder for injection, vial	Calculate according to the dilution used	(>14 y)	(>14 y)	1 g					
P-aminosalicylic acid	200-300 mg/kg in 2 divided doses	PAS acid (4g) sachet	0.5-0.7 g bd	0.75-1 g bd	1-2 g bd	2-3 g bd	3-3.5 g bd	(>14 y)	(>14 y)		Full dose can be given once daily if tolerated
		PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.5-0.7 g bd	0.75-1 g bd	1-2 g bd	2-3 g bd	3-3.5 g bd	(>14 y)	(>14 y)		
		PAS sodium salt 60% w/w (9.2 g, equivalent to 4 g PAS acid) sachet	1.5 g bd	2-3 g bd	3-4 g bd	4 or 6 g bd	6 or 8 g bd	8-12 g bd	8-12 g bd		

Notes and abbreviations: to table (>14 y): follow the separate dose schedule for patients older than 14 years of age; alt: alternate; bd: two times a day; cap: capsule; dt: dispersible tablet; g: gram; im: intramuscular; iv: intravenous; kg: kilogram; mL: millilitre; mg: milligram; M/W/F: Monday, Wednesday, Friday; soln: solution; susp: suspension; tab: tablet

- (Usual upper daily dose) Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.
- (Moxifloxacin 400 mg tab, Linezolid 600 mg tab, Cycloserine 125 mg and 250 mg tab, Ethambutol 400 mg tab) Dissolving in 10 mL of water may facilitate administration in patients in lower weight bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).
- (Linezolid >34 kg) In individuals >44 kg a dose of 600 mg od is proposed.
- (Linezolid 600 mg tbl, Cycloserine 125mg and 250 mg cap) Dissolving in 10 mL of water may facilitate administration in patients in lower weight bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).
- (Delamanid) May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg pediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

- (isoniazid high dose, Clavulanic acid) These agents are only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid). Pyridoxin is always given with high-dose isoniazid in children (12,5 mg od in those aged <5 years and 25 mg od in those aged >4 years.
- (Clavulanic acid) Only available in combination with amoxicillin as co-amoxyclav. Only to be used with carbapenems, in which case they are given together, e.g. 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

Monitoring during STR Treatment

An important factor in DR-TB management is routine monitoring for signs of treatment efficacy and adverse effects of the medications. A successful treatment plan depends upon the intensity and quality of monitoring and supervision activities. Table underneath showing monitoring schedule for treatment response and adverse effects. In case patients die while on treatment, verbal autopsy should be done to clarify the probable cause. Patients on STR should be followed up with smear microscopy and culture 6 and 12 months after the end of treatment.

Table 21 Monitoring Schedule for STR

		Shorter Regimen: Intensive phase						**Shorter regimen: Continuation phase**				
Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
DRTB counseling sessions	X	Sessions 1-3										
Assessment of mental health	X				X							
Evaluation by MDR physician doctor	X	X	X	X	X	X	X	X	X	X	X	X
Adverse drug reactions		X	X	X	X	X	X	X	X	X	X	X
Assesses for TB symptoms	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
BMI	X	X	X	X	X	X	X	X	X	X	X	X
Review contraception	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X											
Smear	X	X	X	X	X	X	X	X	X	X	X	X
Culture	X	X	X	X	X	X	X	X	X	X	X	X
DST 1st line(LPA)	X											
DST 2nd line (LPA)	X			X (If still culture positive)				X (if reversion to positive cultures after initial culture conversion)				
Phenotypic DST	X			X if culture positive at month 3 or reversion to positive after initial culture conversion								
Chest X-ray	X						X					
HIV testing	X											
FBC and neutrophil count if on Lzd†	X	Week 2 and 4	X	X	X	X	X	X	X	X	X	X
Finger prick blood glucose	X											

Creatinine	X	Repeat if baseline Cr was abnormal, or if person is clinically unwell										
K and Mg	X	Repeat if vomiting, diarrhea, if QtcF is prolonged or when patient is clinically unwell										
TSH if on PAS or ETHIO or if Qtc F is prolonged	X			X								
ALT	X	Repeat if vomiting, RUQ pain, jaundice, patient is unwell or any evidence of liver injury										
ECG**	X	X	X	X	X			X	X	X	X	X
Ask about vision & do Snellens monthly while on Lzd	X	X	X	X	X			X	X	X	X	X
**ECG: do at baseline ECG and repeat monthly if on concomitant use of Bedaquiline, Moxifloxacin & Clofazamine. Management of QTC >450 ms is outlined												

Longer DR-TB Treatment (LTR)

In Pakistan NTP has developed ***three*** standardized LTR regimens in order to facilitate implementation, depending on Fq resistance and previous use of SLD (table 22). Within each regimen the exact choice of drugs will depend on DST results and factors mentioned below (including tolerability, previous use of the drug, treatment response).

Table 22 New DR-TB Longer Treatment Regimens

Longer Treatment Regimen - 1 (LTR-1)		**RR-MDR, FQ Susceptible or unknown**
Patient Category	Patient Category	Patient Category
Who do not opt for STR OR Who do not qualify for STR *(*Pregnancy, Drug Intolerance, HIV, Disseminated CNS TB, EP with HIV)*	6 Lfx, Bdq, Lzd, Cfz, Cs, Z/ 12 Lfx, Cfz, Cs, Z	18-month treatment with 16-month post culture conversion. Lzd should be used as long as no serious adverse events emerges and until smear/culture conversion. Lzd or Cs may be replaced by Eto in case of adverse reactions.
Longer Treatment Regimen – 2 (LTR-2): Resistant	**RR-MDR**	**Lfx Resistant and/or Mfx**
Patient Category	Patient Category	Patient Category
Who are confirmed with Levofloxacin and/or Moxifloxacin resistance by LPA or DST	9Bdq, Lzd (6), Cfz, Cs, Z, Am(6*)/ 9Bdq, Cfz, Cs, Z	18-month treatment with 16-month post culture conversion with 6-month initial Lzd and Am for 6 months. Bdq is prolonged until the end of treatment. Lzd should be used as long as no serious adverse events emerges and until smear/culture conversion. * Am can be limited to 4 months if smear/culture has converted.
Longer Treatment Regimen – 3 (LTR-3) confirmed		**MDR Treatment Failure and/or XDR**
Patient Category	Patient Category	Patient Category
Who are declared as "Treatment Failure" either on previous or newly proposed treatments	Individualized salvage regimens advised by national/provincial expert panel. For instance:	20-month treatment with 16-month post culture conversion with 6-month intensive period if injectable is used. Need extensive DST if already Bdq and Lzd

Who are resistant on FQ (Lfx & Mfx) and injectable (Am)	20 Lfx,/Mfx, Bdq, (9), LZd, Cfz, Cs, Eto, Z, PAS, AM(6), Dlm(9) (for failures) 20 Bdq, Dlm, Lzd, Cfz, Cs, Eto, Z, PAS, (XDR confirmed) **Depending on culture conversion, BDQ & Dlm can be continued for 12 months & beyond if there is need (3 Negative cultures not available)*	were used. Select at least Four effective drugs from the available regimen based upon the following principles: Drug Susceptibility testing (DST) Previous drug exposure/regimens Time when previous treatment failed Serious challenges with adverse reactions.

Drugs with reliable test results with LPA and DST

In Pakistan the following tests are done: Molecular for Rif, INH (both *InhA* and *katG*), Fq, SLI. Phenotypic for Bdq, Lfx/Mfx, Lzd, Cfz, Pz. Phenotypic tests are not routinely recommended because they are not reliable to: Cs, E, Eto/Pto, Imp-Cln, Mpm, PAS. Resistance to Pto/Eto can be deducted from molecular test for H-resistance (*inhA* mutation) (see Section 2 for more details about DST).

Basis for selecting and changing drugs in the regimens

- Treatment should be started with **at least four TB agents** likely to be effective. All three Group A agents and at least one Group B agent should be included. At least three agents are included in the continuation phase after Bedaquiline is stopped. If one of the drugs needs to stop because of resistance or adverse reactions, either continue with Bdq after 6 months or add another drug. If only one or two Group A agents are used, both Group B agents are to be included.[3]
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
- **Fully oral regimens** should be the preferred option and injectable agents are no longer among the priority medicines according to WHO. However, in Pakistan SLI is still included in the LTR for Fq-resistant patients, as there are concerns that removing SLI increases the risk of acquired resistance to Bdq and Fq,[4] especially because of the high proportion of RR patients with Fq resistance in Pakistan.
- Treatment **may be started with five agents** to avoid the need to replace a medicine after treatment has started due to:
    - Two of the four agents are likely to be **stopped before the end of treatment**, Bdq at month 6 and Lzd due to toxicity;
    - **Reliable DST** is not available for one or more of the agents but background resistance to the agent is high;
    - The agents included in the regimen are **unlikely to cure** the patient (e.g. only a total of 2 of the agents from Group A and Group B are included in the regimen).

[3] Consideration should also be made to the characteristics of each drug regarding its bactericidal activity, sterilizing activity and prevention of resistance. Each regimen should include one core drug (bactericidal and sterilizing, administered throughout treatment (Fq, Bdq), plus at least one companion drug with high bactericidal activity (SLI, Lzd), a second bactericidal companion drug, plus two sterilizing companion drugs (Cfz, Pz). Companion drugs are used to ensure that no resistance is acquired to the core drug, and thus prevent its loss. *(ref. Van Deun A, Decroo T, Piubello A, de Jong BC, Lynen L, Rieder HL. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. Int J Tuberc Lung Dis. 2018;22(3):239-245. doi:10.5588/ijtld.17.0660).* Resistance to both Bdq and Fq should be prevented, as there is currently no core drug to be included in the regimen (only remaining A drug Lzd is not sterilizing) and cure rates will not be high).

[4] *Chiang CY, Trébucq A, Piubello A, Rieder HL, Schwoebel V, Van Deun A. The looming threat of bedaquiline resistance in tuberculosis. Eur Respir J. 2020;55(6):2000718. Published 2020 Jun 4.*

Ineffective drug (according to DST) may still be included in the regimen but it should not be counted among the target number of medicines needed and **clinical judgment** is advised to decide if the **benefit from its inclusion** outweighs any added toxicity, pill burden, or other downsides

Potentially life-saving treatment should not be withheld until all DST results become available and **empirical treatment with a regimen likely to be effective** may need to be started and adjusted on the basis of DST results once they become available

Choice of Drugs for Longer DR-TB Treatment Regimens:

Bedaquiline should be included in patients aged 18 *years* or more. However, Bedaquiline may also be used for patient 6-17 years.

Delamanid may be included in patients ***aged 3 years*** or more.

Amikacin should only be used if susceptibility is confirmed and facility to monitor closely ototoxicity and immediate change with Lzd if any abnormality to prevent ototoxicity. Intermittent use may be considered from the start.

INH high-dose may still be used unless mutations to *katG* that confer high level resistance to isoniazid.

Use of Bdq and Dlm alone or in combination beyond 6 months should follow practices on "best practices" and may be used as "**off label**"

In patients on regimens without an intensive phase containing injectable agents, the treatment duration is determined by **total duration and time after culture conversion[5].**

The **total duration for DR-TB treatment** in 18-20 months may be modified according to the patient response to therapy. In regimens containing an injectable the **intensive phase is of 6 month**s with total treatment duration of 18 months with 16 months after culture conversion. The duration of treatment post culture conversion may be modified according to the patient's response to therapy (e.g. culture conversion before 2 months of treatment) and other risk factors for treatment failure or relapse

Extension of intensive phase: The initial phase of 6 months may be extended to 8 months (and total to 20 months) in the following situations:

- A slow clinical response to treatment with failure to gain weight, failure of chest X-ray resolution, delayed smear/culture conversion.
- Bilateral pulmonary disease with extensive cavitation
- Delayed culture conversion (positive culture at 4th months)
- When FQ susceptibility is not confirmed on LPA

DR TB treatment in children <14 years of age.

Use of Bedaquiline (down till 6 years of age) and delamanid (down till 3 years of age) is recommended.

Injectable free regimen is desirable - young and with mild disease (absence of malnutrition, serious forms of extra pulmonary disease, cavitation on chest radiography or HIV infection). Regular audiometry to detect hearing loss if injectable is given**.**

High-dose isoniazid in pediatric regimens is associated with treatment success.

In children shortening total treatment duration to less than 18 months may be considered in the case of children without severe disease. Use of amikacin or streptomycin in children should only be resorted to when other options are not possible, when testing confirms susceptibility and the possibility to monitor for ototoxicity and nephrotoxicity is present

[5] Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. (ref. WHO Definitions and reporting framework revision 2013 updated Nov 2014, p. 7)

In bacteriologically negative and extra pulmonary patients, a total duration of treatment of 18-20 months is advised and the response should be monitored by clinical parameters other than specimen bacteriology.

Pregnant women: injectable agents and Ethionamide are contraindicated in pregnancy. There is little knowledge about the safety of Bedaquiline and delamanid in pregnancy and while breastfeeding. (See Section 7 for more information on pregnancy)

The different outcomes of RR treatment are described in section 12 Monitoring and evaluation. One of the outcomes is failure.

Principles of treatment with LTR:

- The treatment should be "person-centered", informing and counselling about the disease and treatment at start and when needed, agreeing with the patient the most practical way to directly observe the treatment (DOT) and regularly follow-up and provide support throughout the treatment period (see Section 6 education and DOT).
- Patients should be carefully monitored with monthly smear and culture (two samples each time). If culture is positive at month 3 or later, it should be sent for LPA and DST to detect acquired resistance, especially to Fq and Bdq. (see paragraph on monitoring later in section)
- Vigilant monitoring with implementation of an effective aDSM component is needed to timely detect and manage adverse events. (See paragraph on monitoring later in section).

Management of failure in LTR treatment

a. Treatment Failure signs:

Multiple Factors need to be analyzed before declaration of "treatment failure outcome" in MDR TB. For definition of "failure" in M&E, see Section 1 Introduction, definitions. Some points indicating imminent signs leading to potential treatment failure are as follows:

- Clinical, radiological and bacteriological evidence of progressive disease after 6 months of treatment
- Persistent positive smear/culture in the intensive phase 6 months. (fail to achieve culture conversion in intensive phase)
- After culture conversion, two consecutive positive cultures at least 1 month apart (reversion[6]) in continuation phase;
- Extensive and progressive lung disease excluding option of surgical treatment
- Reappearance (resurgence) of disease after 6 months of treatment
- Clinical deterioration (e.g. respiratory insufficiency; intolerable side-effects
- Resistance to second-line drugs leaving no option for a regimen with effective drugs.

Culture is more useful than smear taken as evidence of failure.

1. A single positive culture in the presence of good clinical response could be due to laboratory error. A subsequent negative culture or decreasing colony counts will indicate a good response to present treatment.
2. Positive smear with negative culture may be due to dead bacilli, delay in sputum transportation (bacilli die on the way) or NTM .
3. Repeated smear- and culture-negative results in a patient with deteriorating clinical and radiological states may indicate a disease/course other than DR-TB.

b. Assessment of patient failing DR-TB treatment.

Some of the factors to check before declaring a treatment failure are as follows:

1. Confirmation of adherence to treatment by checking the treatment card and discussion with the patient and DOT provider on:
    - Interference to adherence caused by socioeconomic status

[6] Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase. (ref. WHO Definitions and reporting framework revision 2013 updated Nov 2014, p. 7)

- Interference to adherence caused of adverse effects by anti TB drugs
- Verifying provision of treatment under DOT. The treatment card should be reviewed to confirm that the patients fully adhered to correct treatment as per prescription. An informal interview should be taken place to elicit any underlying causes. This may occur in absence of DOT provider to rule out any influence by him/her. If manipulation is suspected, the DOT provider should be changed. He/she should receive additional training and be closely supervised by his/her supervisor whenever he/she is assigned as another DOT provider's role again. If the DOT provider fails to fulfill his/her duties for second time, she/he may be removed from the task.

2. Exclusion of comorbid conditions that will affect drug administration or immunological competency (e.g. chronic diarrhea, NTMs, fungal infections, lung infections, or a pulmonary malignancy, illnesses that may decrease the absorption of medicines (e.g. chronic diarrhea), immune suppression (e.g. HIV infection). History of glycemic control and effectiveness of DM management for MDRTBDM cases. Timely initiation of ART, drug-drug interaction between anti-TB drugs and ART.
3. Review of current regimen in light of fresh DST and medical history. Appropriateness of dose of medication for existing body weight. The bacteriological data should be reviewed.

c. Change of Regimen:

If the current regimen seems to be inadequate, a new regimen **(LTR-3)** containing at least four effective drugs should be designed. The current treatment should be declared as a treatment failure and the patient should be re-registered. Adding one or two drugs to a failing regimen should be avoided.

d. Termination of treatment because of failure:

It takes 3-4 months to evaluate effectiveness of a treatment regimen. However, continuation of ineffective therapy would lead to increased patient burden in term of experiencing unnecessary side effects, undue cost impacts and acquisition of additional resistance specifically to second line drugs. For treatment suspension it is necessary to make the patient understand and accept the withdrawal of treatment. The final decision to terminate a treatment must rest with DR-TB committee.

e. After termination of DRTB treatment because of failure:

- Supportive care is the only option left after suspension of treatment.
- Ensure clinical and bacteriological follow-up of the patient every 3 months.
- Adequate nursing care and symptomatic relief if patient is severely ill (e.g. in certain circumstances hospice care and nursing home care may be seriously considered).
- Nutritional support (if budget available) or linking the patient to NGO support.
- Psychosocial support and continuing health education (by government counseling staff or by NGO peer educators/counsellors).
- DR-TB treatment termination is **not abandonment of the patient**
- Strict infection control to prevent further spread of disease to other contacts
- **Palliative Care Counselling session** aims to gently inform patients and their families about their condition and their prognosis. This session provides practical information on the clinical management of the patient (whether or not treatment has been withdrawn) and guidance on how to access palliative support services. [7]

Monitoring of DR-TB Patients on LTR

An important factor in DR-TB management is routine monitoring for signs of treatment efficacy and adverse effects of the medications. A successful treatment plan depends upon the intensity and quality of monitoring and supervision activities. Table 23 shows monitoring schedule for treatment response and adverse effects. Here are some key principles:

[7] From DR-TB guidelines 2019 p 30

- All patients to receive routine counselling to identify and address factors contributing to non-adherence by the patient.
- Sputum smear and culture must be taken at every month – one sample for smear and one sample for culture
- Vigilant monitoring is needed to identify any decrease in CBC profile (HB>8g/dl, neutrophils <0.75x10^9/L or platelets <50x10^9/L.), loss of visual acuity and peripheral neuropathy. If a patient exhibit any of the signs mentioned above or decrease in blood count, Lzd should be stopped.
- ECG should be done monthly providing management if corrected QT interval by Fredricia QtcF ≥450 (see Annex 7 for details)
- In patients who are developing clinical psychosis or depression, STOP Cycloserine and refer the case to Technical Review Panel (TRP).
- If LPA second line or phenotypic DST shows FQ resistance, then the treatment must be shifted to LTR-2 or LTR-3
- In case patients die while on treatment, **verbal autopsy** should be done to clarify the probable cause

Sputum conversion beyond 4 months or culture reversion must be properly managed while extending the initial phase duration to 8 months. A repeat DST should be requested while providing full social support to improve treatment adherence. The patient is to be presented to National MDR committee if failure is suspected.

Table 23 Monitoring schedule for treatment response LTR

Monitoring Schedule for LTR																			
		Initial Phase						Continuation phase											
Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-20**
DRTB counseling sessions	X	Sessions 1 - 3			X														
Assessment of mental health	X				X														
Evaluation by MDR physician doctor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse drug reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assesses for TB symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																		
BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review contraception	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X																		
Smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DST 1st line(LPA)	X				X(If still culture positive)			X (if reconversion to positive cultures after initial culture conversion)												
DST 2ndline (LPA)	X				X(If still culture positive)			X (if reconversion to positive cultures after initial culture conversion)												
Phenotypic DST	X if LPA second line resistance (reflex)				X if culture positive at month 4 or reconversion to positive after initial culture conversion															
Phenotypic FLQ sensitivity	Reflex if second line LPA is FLQ susceptible																			
Chest X-ray	X						X													
HIV testing	X																			
FBC and neutrophil count if on Lzd†	X	WK 2 & 4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Finger prick blood glucose	X																			
Creatinine	X	Do monthly if on injectable agent. Otherwise repeat if baseline Cr was abnormal, or if person is clinically unwell																		
K and Mg	X	Do monthly if on injectable agent. Otherwise repeat if vomiting, diarrhea, if QtcF is prolonged or when patient is clinically unwell																		
TSHif on PAS or ETHIO or if QtcF is prolonged	X			X																
ALT	X	Repeat if vomiting, RUQ pain, jaundice, patient is unwell or any evidence of liver injury																		
Audiometry*	X			X	Monthly if on injectable. If any changes in audiometry should be referred for Audio management & care (stop injectable)															
ECG**	X	X	X	X	X	X	X			X			X			X			X	
Ask about vision & do Snellens monthly while on Lzd	X	X	X	X	X	X	X	x	x	x	x	x	x	x	x	x	x	x	x	

† FBC and differential count (neutrophil count) before starting Lzd, and then at 2 and 4 weeks and then monthly while on LZD

*Audiometry: If receiving an injectable audiometry should be done MONTHY.

**ECG: do at baseline ECG and repeat monthly if on concomitant use of Bedaquiline, Moxifloxacin & Clofazimine. Management of QTC >450 ms is outlined

c. Post treatment monitoring:

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

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

As relapse of TB may happen in cured RR-TB patients, they should be instructed to consult the clinic if they experience TB specific signs and symptoms again e.g. cough for two weeks, weight loss, fever, etc. If the patient shows any signs of TB, he/she should be assessed for second line DST to diagnose XDR and initiate treatment accordingly.

If the patient has stopped treatment before completing the recommended full treatment,
the patient should be traced and assessed every 6 months for at least 2years to detect signs and symptoms of TB, to do investigations and re-treatment if indicated.

Procedures for Enrolment of DR-TB patient on treatment at the PMDT site

Upon arrival of the patient to the central or district PMDT site, the patient meets with the DR-TB treatment Coordinator and TC review the following required documents:

- A referral letter.
- Previous Chest Radiographs (CXR) and any other medical documents from any relevant centers.
- An ID card, two contact phone numbers, and complete address information**.**
- An official report of the result of the Gene Xpert, sputum **culture and DST** if available. All cultures and DST must be done in a laboratory which is certified **(EQA).**

Next step is to meet with the DR-TB physician to take history and physical examination, if eligible selection of appropriate treatment regimen and decision to start treatment, Fill relevant section of DR-TB01 card, Educating the patient about DR-TB treatment and preparing prescription to pharmacy for collection of 15 days medicine.

Afterwards the patient meets again with the Treatment Coordinator

- Complete all the remaining sections of the DR-TB treatment card.
- Arrange for submission of specimens for Month 0 sputum, blood, chemistry, visual and audiometry testing
- Coordinate with the PTP, EDO, DTC/DTO and other concerned offices to Identify and contact the nearest BMU or make arrangement to ref: nearest district PMDT.

Patient's Follow Up Visit to the nearest DOTs center (BMU, BHU/health facility etc.)

Treatment Coordinator at the PMDT in collaboration with PTP, DTC/DTO must have identified nearest DOTS center from the already available list of DOTS center to the patient's residence (BMU, BHU, PHC, etc.) and all the necessary logistics have been settled for a proper linkage with the patient and treatment supporter.

The patient, accompanied by the treatment supporter, should visit this nearest DOTS center/ health facility ON A WEEKLY BASIS for the following tasks:

- Monitor the patient if having any signs or symptoms of adverse reactions
- Managing minor side effects without making/suggesting any changes in the DR-TB treatment
- Referral to the PMDT site in case of major side effects
- Update the patient's copy of the DR-TB #01 treatment card with any adverse event
- Advise and emphasize the monthly follow up visit to PMDT site along with treatment supporter

Patient's Follow Up Visits to the DR-TB Health Care Facility after the Intensive phase

During intensive phase the MDR-TB patient carries out monthly follow up visit to the PMDT site along with treatment supporter. After the discontinuation of the intensive phase, the DR-TB patient, accompanied by treatment supporter, is expected to visit the DR-TB Treatment Site (PMDT) every month for the Follow Up.

End of Treatment

The treatment of a DR-TB patient is considered to be completed if the patient meets the criteria the treatment outcome will be declared by DR-TB physician at PMDT site

Management of TB Meningitis

- Tuberculosis meningitis is the deadliest form of TB with highest mortality in children.
- Treatment guided by DST and ability of drug to cross blood-brain barrier (Drugs that can **penetrate CNS** are Levo, Moxi, Eto, Pto, Cyc.Tzd, Lzd and Imp-cil).
- Every effort should be made to ascertain TB drug sensitivity results for CNS disease (contact history, sending cerebrospinal fluid for GeneXpert/culture and sensitivity as well as taking TB diagnostic and sensitivity samples from other sites (sputum, lymph node, etc.).
- In children **Meropenam** is preferred over Imp-cil due to higher chances of seizures with the later drug.
- **INH (High dose) and Z** can also reach cerebrospinal fluid if strains are susceptible.
- **Drugs not penetrating CNS** should not be counted as effective drug for DR-TB meningitis (**PAS, E**)
- **Am & S** only penetrate CNS in the presence of meningeal inflammation
- There are few data on the CNS penetration of clofazimine, bedaquiline or delamanid.
- Steroids can be given and have proven mortality benefit
- In patients co-infected with HIV and not on antiretroviral therapy (ART): ART should be initiated 4-6 weeks after TB treatment (to minimize the risk of life-threatening intracranial IRIS). Persons already on ART should continue ART throughout TB treatment.

Table 24 Core second line drugs for TB Meningitis.

Levofloxacin	10-15 mg/kg	Throughout the treatment
Moxifloxacin	400 mg	Throughout the treatment
Ethionamide	15-20 mg/kg; max 1g	Throughout the treatment
Amikacin	15-30 mg/kg; max 1g IV or IM	Intensive phase only
Cycloserine	10-15 mg/kg; max 1g	Throughout the treatment
Linezolid	600 mg	Throughout the treatment

Surgery in DR-TB:

The most common operative procedure in patients with pulmonary DR-TB is surgical resection (lobectomy or wedge resection). It is considered to be an adjunct to chemotherapy. It is to be offered alongside the recommended DR-TB regimen. Surgery is not indicated in patients with extensive bilateral disease. Generally, at least two months of therapy should be given or culture conversion obtained before surgical resection to decrease the bacterial infection in the surrounding lung tissue. The DR-TB regimen should continue without interruption except for the immediate one or two days during the postoperative period. General indications for surgical resection include patients who remain sputum positive (smear and/or culture), with resistance to a large number of drugs, and have localized pulmonary disease.

Section 5:

DR-TB Patient Education, Counselling, DOT Provision and case holding

Education and counselling of DR-TB patients

Health staff need to communicate with the DR-TB patients from the start to help them cope and agree to complete the necessary tests and treatment in the best way. There should be standards (folders, posters) about who should provide information, how it should be provided and the main message. Different categories of health staff will educate and inform the patient while counselors/psychologist councils the patient in the PMDT especially on adherence.

Before Xpert test

The health staff filling in the request form for Xpert (BMU doctor, nurse) should inform the patient:

- where and how to collect sputum, test, quality & minimal amount of the sputum required, where the Xpert MTB/RIF test is done; when and how the result will be received, what results can be and subsequent likely actions to be taken
- Why it is wise to do the test: Early detection and initiation of TB treatment is prevention of spread of tuberculosis to family members & close friends and relatives and completing the treatment will cure the patient.

When result of Xpert test comes showing Rifampicin resistance

The health staff receiving the result showing Rif resistance should explain:

- The test should be repeated with a new sample in the same lab except when the patient was treated for TB before, or was in contact with a known DR-TB patient.
- When the test is confirmed (unless previously treated or contact to RR patient), the patient need to go for consultation in the nearest PMDT site or decentralized district DR-TB site. The DR TB patient should have an informed choice where to be treated for DR TB treatment, as some patients may opt for a PMDT site away from their place of living for different reasons including stigma. It is a costly treatment but all expenses (including transport) will be borne by NTP (as per logistical arrangement).

Pre-treatment education and counselling in PMDT site

Education and information will be provided by all staff members when they meet the patient (MDR physician, treatment supporter, pharmacist, and psychologist) when they meet the patient one by one at various steps. The health staff in the PMDT site should explain:

(a) Plan of treatment, drugs to be used and likely course in an understandable language.
(b) The needs of the investigations including blood test and psychological test before SLD treatment.
(b) It is a costly treatment but all expenses will be borne by NTP. Social & some financial support will be available during treatment.
(c) Information on how to live at home/workplace, minimizing risk of spread to close family members and friends.

The psychologist/councilor in the PMDT will do **First time counseling** (initial session). This can be done in or equivalent to pretreatment counseling. Counselor has to discuss on

- Patient's general health, history of smoking, drug abuse, alcoholic, HIV disease, pregnant or not (see also section 6 Contraception)
- Important of regularity of drug taking and unfavorable outcome of irregularity of drug taking
- Number of drugs to be taken, doses, frequency, duration and adherence during treatment.
- To consult to physician if the patient suffers any S/E
- baseline and monthly laboratory investigations,
- Drug collection system and Follow up examinations

- To make sure the date for 2nd counseling section

Adherence Counselling

Adherence is based on an agreement between the patient and the health care team, and the patient's own agreement to play an active role in his/her health care. Method of motivational-interviewing is used for adherence counseling. Essential ingredients of this strategy of counseling include:

1) Building engagement (Alliance of Work)
2) Identify the problem/difficulty
3) Clarify to get better understanding
4) Action to solve problem/difficulty

Adherence means following the treatment with own autonomy.

Assessing Motivators and Barriers to Adherence:

(a) Medical Factors – understanding & experience of illness and treatment, health problems, side effects, relationship with health provider.
(b) Social/Family Factors – Level of relationships, caregivers/ dependents, living situation.
(c) Economic Factors – income, work, housing.
(d Psychological Factors – Attitude toward illness/life.
(e) Mental Health – depression, anxiety, intellectual capacity.
(f) Alcohol/Drug Use – past/present, frequency, amount, type.
(g) Discrimination – stigmatization, disclosure

Counsellor should constantly be assessing changes in motivation from one assessing to the next. Treatment Adherence counseling should be practiced at least 3 times before & during initial SLD treatment. It should be done at each follow up visit.

(b) **Second time counseling** (preparation to start treatment), counselor has to discuss on

- Remind the facts discussed in previous 1st time counseling session
- Give new information on the investigation & treatment
- Discussion on the problems the patient asks and find the possible solution

(c) **Third time counseling** (confirm readiness), counselor has to discuss on

1. Remind the facts discussed in previous 2 times counseling sessions
2. Discussion on the problems the patient asks and finds the possible solution

Special attention to must be given to:

- Previously defaulted patients
- Prisoners
- Patients without family support
- Patients with past history of taking second line anti-TB drugs
- Patients with history of adverse drug reactions
- Patients with co-morbidities
- Patients with addictions to alcohol or other drugs

Following areas must be covered in counseling.

A Socio-economical and psychological support:

The psychological and physical fatigue along with some out of pocket expenditure can lead to mistrust in the health system. Similarly During the treatment, patient may face many psychological problems like anxiety, depression. Combined with lower socio-economic status of many patient and psychological problems, these may result in non-adherence and eventually loss to follow up. On treatment patients must receive psychological, financial and nutritional support throughout the treatment cycle to address the treatment related issues.

B Patient Confidentiality

It is the responsibility of MDR team to maintain patient confidentiality regarding the nature of the disease as much as possible. This will help to create a trustworthy environment between patient and treatment center and also improve treatment adherence. This should be practiced not only at the health facility but also during home visits by the PMDT / District Team. The PMDT / District Team should not wear white coats or identity cards during home visit. The conversation with the patient and his treatment supporter must be done in a separate well ventilated room.

C Health Education:

It is important to properly educate the patient and their families regarding the nature of disease, diagnostic process and treatment plan. Any confusion or concerns on patient's part must be properly addressed in a friendly and supportive way.

- Information on spread of disease and how to stop the transmission.
- Family members must also be taken into confidence especially to address and mitigate stigma.
- Patients most likely will be anxious, and need reassurance that the disease is curable. Patients and family may be informed regarding unfavorable outcomes but not in a discouraging way.
- The patient needs to have information on type of medicines, treatment process and necessity of directly observed treatment.

It is crucial to obtain the consent (verbal or written) of the patient to undertake DR-TB treatment under DOT throughout the length of treatment cycle. Daily visits by treatment supporter for DOT offer many opportunities to provide information, support, and answer the questions the patient might have about prevention, diagnosis and treatment.

The health worker may need to give repeated encouragement to patients who feel that daily treatment is too time-consuming and inconvenient.

Education/information during weekly monitoring visits to local BMU

These visits to BMU doctor are planned to be routine as part of more decentralized management of DR-TB, where DR-TB treatment may start in district center. Special focus will be on detecting and managing side effects and addressing any adherence problems.

Education/counselling during monthly monitoring visits to PMDT sites

The physician at the DR-TB management center will also provide information and motivation to the patient during these monthly monitoring visits.

Interpersonal communication:

Interpersonal Communication is face to face verbal or non-verbal exchange of information and feelings between two or more people. It is a Two-way process of reaching mutual understanding. Good communication is an essential part of good quality care. Many TB patients are poor, with very little money to use on health care. If the quality of care provided in our health facilities is of a low standard, patients may turn to unqualified healers which may result in inadequate treatment. Good communication is needed not only to inform patients of important messages about DR-TB and its treatment but it is also critical to encouraging patients to return for the next treatment visit, day after day and month after month. Principles of effective communication is described in annex 8 with the acronym WELL= Welcome the patient, Encourage your patient to talk, Look at your patient, Listen to your patients.

DOT provision and case holding

DOT refers to Directly Observed Treatment where the Treatment Supporter of the patient is responsible to ensure (through observation) that the patient has taken his medicine as prescribed. This not only ensures adherence but also facilitates to early detect adverse effects.

Treatment Adherence

- All patients should be supervised for intake of TB medicines.
- All patients should be monitored, to assess their response to therapy.

- Regular monitoring of patients also facilitates treatment completion.
- Regular monitoring allows the identification and timely management of adverse drug reactions

(1) **Ambulatory treatment with home based DOT**: This is the preferred option. The following requirements are to be met among patients who are having treatment in the community:

- Household is ready to receive the patient
- DOT provider/Treatment supporter identified
- Place for follow up care with doctor in local BMU
- Transportation for monthly follow up at PMDT site/decentralized DR-TB site.
- Socioeconomic support

(2) **Hospital based treatment**: Hospitalization should be avoided unless really necessary and kept as short as possible since it increases risk of infecting others and being infected (also from Covid-19 during pandemics). The criteria for hospital based treatment are limited as follows:

- Patient is clinically and physically unfit to receive care at home
- Severe side effects
- Problems with adherence due to multiple social issues in patients' families endangering treatment success
- Severe co morbidities (HIV, DM, Renal failure, liver failure, anemia etc.)
- Failing DR-TB TB treatment regimens
- DRTB patients should be kept separated from other non-DR-TB patients or in single room.
- Proper infection control at wards to reduce spread of transmission
- Upon discharge patient must be handed over with sufficient drugs until next appointment in PMDT site, treatment card copy, and MDR TB referral form.
- Pregnant women and children do not need to be hospitalized if clinically stable.

Directly Observed Therapy (DOT):

DOT is the strategy to make sure the patient is taking the TB medicines correctly and for entire duration of treatment, so that the bacilli do not become resistant to the drugs and also to quickly detect and manage side effects. **DOT is especially important in DR-TB because DR-TB is more difficult to cure, requiring second line drugs with more side effects, and which must be taken correctly and during an even longer time than DS-TB.** The patient swallows daily dose of treatment under the direct observation of a treatment supporter. DOT is one of the key components of DR-TB-TB management. One of the following options for DOT should be agreed with the patients:

- Community- or home-based DOT with trained health-care workers as treatment supporters.
- Video observed treatment (VOT) via video communication technology (cell phone, tablets, pc) where health staff communicates with patients who can use this technology. Also reminders via phone can be very helpful.
- Facility based DOT for patient living within reasonable walking distance from a facility where drugs can be taken daily under DOT without much delay, risk of infecting others and being infected (especially during Covid-19).
- If none of the above options are possible, the last resort is community- or home-based DOT with family member as treatment supporter.

The strategy to observe treatment (DOT) is implemented at all TB Care Facilities in the country.

- Treatment services should be provided as close to the patient's home as possible.
- Patient should select a treatment supporter who will observe the daily intake of drugs.
- The treatment supporter identified by the patient will be briefed about the protocols of observing the intake of drugs, such as dosage, timings, with or without food etc.
- DOT should be done at a time and place that is convenient for the patient.

- The treatment supporter accompanied by patient will collect the drugs on monthly basis from PMDT site or decentralized DR-TB site.
- The treatment supporter accompanied by patient will go weekly for consultation with the doctor at the agreed BMU especially to monitor and manage side effects
- The treatment supporter accompanied by patient will go to the nearest BMU (or PMDT site) in case of adverse events.

Explain DOT and importance of Treatment adherence

- It is important that you take your drugs every day, for the whole treatment period (usually 11-18 months).
- You must keep taking the tablets so that you get cured.
- You may forget to take medicine, especially when you are feeling well and go back to work.
- We recommend that we agree on a Treatment supporter to encourage you, and watch you take your tablets every day. In this way you do not forget to take the tablets.
- The treatment supporter will help you to take the right pills in the right dose for the right length of time.
- You can tell your Supporter if there are any side effects of the medicines, and they can go with you to the clinic.

Informed consent must be acquired from Patient on agreement on organization of DOT signed by the patient and treatment coordinator in the PMDT. Clinical staff is responsible to obtain this agreement. DOT should not place as little burden as possible on patients and their families; therefore, DOT must be conducted in the place where it is most convenient for the patient.

Helping the patient to select a treatment supporter

Identification of a suitable and acceptable treatment supporter for the patient is the key to success of directly observed treatment. The treatment supporter should be:

- Accessible, living near enough the patient to visit daily
- Reliable, having the trust of both the patient and health staff involved in DR-TB
- Accountable to health services
- Caring but capable of having a good influence on the patient.

The available treatment supporter options generally includes:

- Health facility based worker (HFW)
- Lady health worker(LHW)
- Community health worker(CHW)
- Community volunteer (CVT)
- Family member (FM).

Principles for DOT

<u>The DOT provider should follow the following procedures:</u>

- Time of DOT should be permanent, agreed in advance, and the Treatment supporter should note it on the patient's DR-TB Treatment Supporter Card which is kept by the Treatment Supporter.
- The patient should keep the appointed time for taking drugs with the DOT provider.
- The prescribed medications are taken under direct observation and the whole daily dose is taken in one sitting, unless the physician indicates that medicine can be split up. (Pyrazinamide, injectable agents and FQ are always given in a single dose. Ethionamide, Cycloserine and PAS are normally given twice a day to reduce side effects. Delamanid should also be given twice per day.)
- Treatment is administered in the same designated place, according to the schedule, keeping the same sequence.

The Treatment Supporter

- The treatment supporter should lay out the pills and check the dosage
- Before handing over the medicines, the DOT Provider should ask the name of the patient, check the note on the vial or the plastic bag containing the patient's pills.
- The injection should be given at the same time as oral drugs.
- The injection is to be given by either a trained nurse or doctor. A test dose, at the start of treatment, is required for injection and should be given at a TB center or hospital. The injection must be followed by oral intake of SLDs.
- The patient, standing or sitting in front of the responsible person, should swallow the drugs immediately.
- After swallowing the tablets, the patient drinks some water. The patient should show their mouth, palms and cup to the DOT Provider. If the patient does not do this, the DOT Provider should ask the patient to do so.
- The next patient can be served only once the Provider is sure that the previous one has taken all their medicines.
- If the patient is absent and/or does not take the drugs, the DOT Provider should inform (by phone) the treatment coordinator center by the end of the working day; the treatment coordinator reports all missed doses to the MDR physician within one working day.
- If side-effects occur, the DOT Provider should inform the treatment coordinator immediately.
- Treatment coordinators are responsible for managing minor side-effects and referring to the MDR physician if major side-effects occur.

Role of Treatment Supporter

The identified Supporter is explained the importance of support to a patient and asked if he/she agrees to take responsibility for supporting the patient.

The treatment support role is comprised of the following seven essential components:

- Collect tablets, on monthly basis, and safely store, preferably with the patient
- Directly observe intake of tablets (in right number of drugs and dosage)
- Record daily intake of drugs in Treatment Support Card
- Remind patient to visit BMU/TB Care Facility weekly and the PMDT site monthly
- Identify possible side effects and refer to BMU?
- Discuss difficulties in continued treatment and help to resolve them
- Trace and help to retrieve late patients

Responsibilities of Treatment Supporter

Collection and storage of drugs

During the whole treatment period, patient along with treatment supporter should collect the drugs from PMDT from which the patient is enrolled. The drugs must be stored in a safe place (under lock, if possible) and out of reach of children. In addition, the storage place should be dry and cool. The medicines are usually kept by the patient.

Observed intake of tablets

It is important for the Treatment Supporter to understand clearly the number of tablets to be taken by the patient, on daily basis. This is usually done by the pharmacist at PMDT/decentralized site telling and showing him/her the tablets to be taken daily.

The patient under DOT is expected to take maximum number of doses under supervision. However, occasionally the patient will face situation where he/she will not be able to contact Supporter for one or more days for observed intake (for instance during emergencies such as covid-19 and important family events). The Supporter is then expected to instruct the patient about intake of tablets and give the tablets for the requested number of days.

Record daily intake in treatment support card

The TB Program Pakistan has designed a Card for Treatment Supporter to record daily intake of drugs. Three symbols used to record "supervised intake", "unsupervised intake" and "missed intake" of tablets are same as used in TB01 records. The Treatment Support Card will be kept with the Treatment Supporter, who will keep record of the patient's daily intake of tablets.

Follow-up visit to the BMU/TB Care Facility:

Treatment Supporter is explained the importance of monthly follow-up visit to **PMDT.** This follow- up visit is important for the patient because he/she is assessed clinically, his/her sputum is examined and drugs are changed accordingly. The recorded date of appointment at PMDT and the nearest BMU (for weekly visit). TB02 helps to know when to send the patient.

Identify side effects and refer: The Treatment Supporter is expected to monitor appearance of symptoms or complaints, which can potentially be due to side effects of the TB drugs. In all such cases the Supporter is expected to refer the patient, as earliest as possible, to the doctor at PMDT site

Identify and retrieve late patients: The Treatment Supporter has a key role in the early identification of interruption of drug intake and refusal to continue treatment. The Treatment Supporter should be the first person to try to convince and help the patient to continue in case of interruption or refusal. If a patient persistently refuses to continue treatment or has complaints related to the taking tablets, the Treatment Supporter should bring the patient to the nearest BMU. If minor issue, then the BMU can manage itself. If serious issue, then the patient will be referred to PMDT Site or decentralized site (DHQ) PMDT site.

Adherence to Treatment:

Adequate supportive measures in the form of travel allowance and monthly payment for nutritional support for DR-TB-TB patients and only travel allowance for DOT providers should be in place to prevent non adherence.

Follow up of non-adherent patients

Tracing mechanism must be initiated within 24 hours of a missed-dose patient. If a hospitalized patient leaves the hospital during an admission period, the MDR physician & treatment coordinator are responsible for initiating the mechanism to trace the patient. The tracing mechanism can be conducted by the Treatment Coordinator of the PMDT / decentralized site. MDR physician in-charge can contact the district health Authority /District TB Coordinator for support. The District Health Authority will facilitate through engaging the local BMU Staff and outreach teams along with the treatment coordinator of the PMDT Site.

The protocols for follow up on non-adherent patient are found in Annex 9. In any case, the regional health center should be informed about non-adhering patients.

In case of missed doses by an ambulatory care patient, the DOT Provider will report all missed doses to the treatment Coordinator, or if the patient is not able to report at the prescribed date for treatment or follow-up examination. The treatment coordinator is responsible for tracing the patient for missed clinic appointments

How to prevent Lost to follow-up

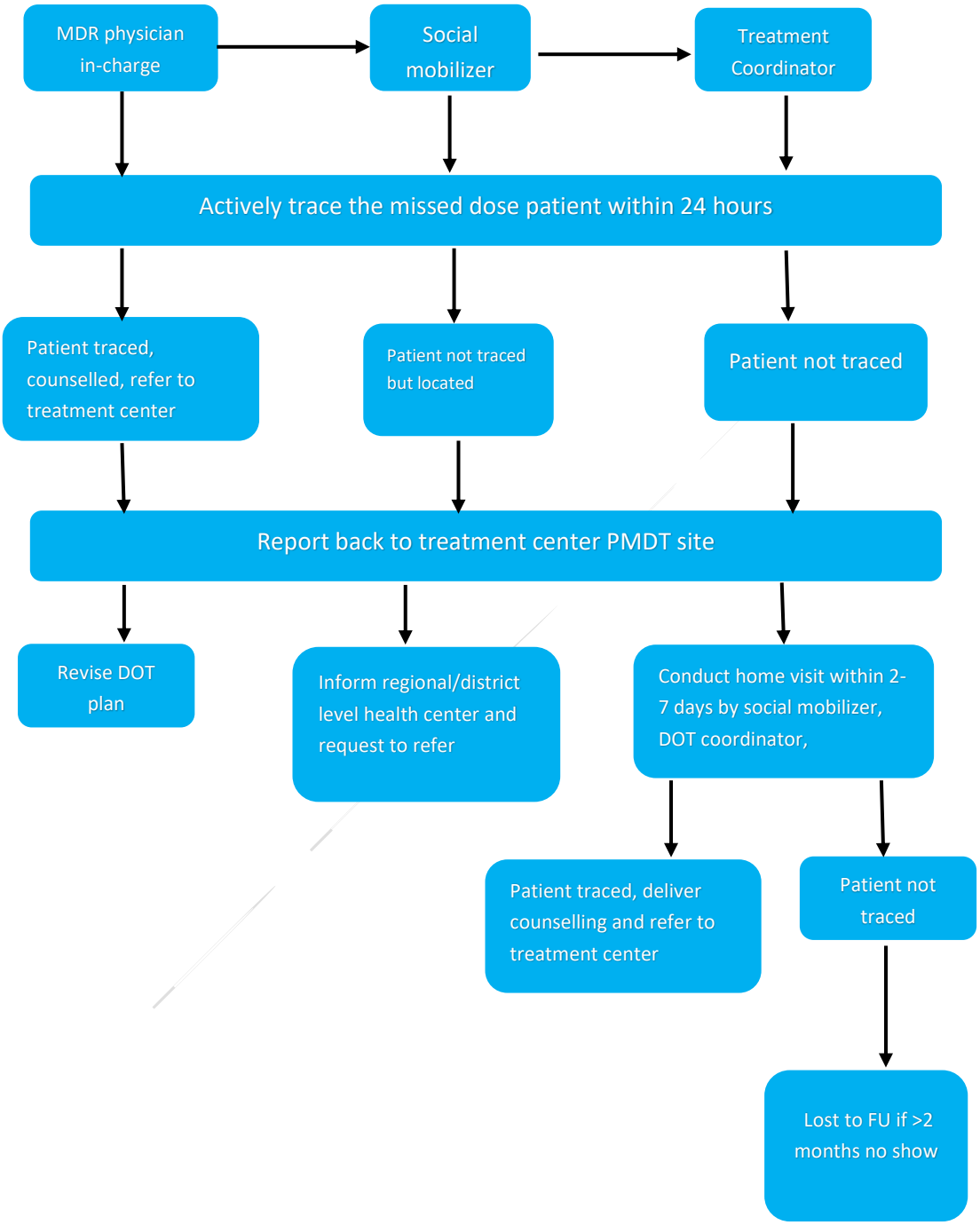
The best is to prevent loss to follow-up. There are a number of strategies to prevent patients from being lost from follow-up:

- Complete early patient education about illness and patient's role in treatment success.
- Training and psychological preparation of the patient for treatment and possible manageable side-effects and ways of managing them.
- Creating DOT conditions convenient for the patient (including phone numbers for easy access?).
- Provision of social and economic support: counseling and travel allowance/nutritional support.
- Counseling session administered before discharge.

- Patient supplied with drugs through DOT Provider, treatment card, referral form, travel allowance and nutritional support.

The tracing mechanism for patient who have missed a dose of DR-TB treatment is described in figure below:

Figure 11 Tracing mechanism for patient who has missed a dose of DR-TB treatment



Once a patient has been traced, the situation should be handled in a sympathetic, friendly and non-judgmental manner. Listen to the patient's reason for missing a dose(s) or being lost from follow-up, and work with the patient and family to ensure continuation of treatment, while encouraging the patient not to default again.

Section 6:

MDR management in Special Conditions

The clinician and the DR-TB managing team must take a complete history of the patient at time of enrollment with special focus on special conditions which may affect the treatment regimen and outcomes. Additionally, the patients must be regularly counselled regarding these conditions during the course of treatment.
This chapter outlines the management of Drug Resistant TB in selected special conditions and situations.

Pregnancy:

Pregnancy is not contraindicated in active MDR treatment. A pregnancy test must be done on all females of child bearing age as part of initial assessment.

The risks and benefits of treatment should be carefully considered, with primary goal of smear conversion to protect both mother and fetus. The decision to start MDR treatment in pregnant females must rest upon the following guidelines:

- If condition of mother is mild or moderate: start treatment in 2nd trimester (to avoid teratogenic effects in 1st trimester)
- If condition of mother is severe: start at once (clinically judgement based upon severity of disease and presence of life threatening signs & symptoms.
- STR Short term regimen should not be used.
- Ethionamide should be avoided as it aggravates the symptoms of morning sickness (nausea & vomiting) and because animal reproduction studies have shown an adverse effect on the fetus.
- Avoid injectable drugs
- The total duration of treatment will be the same as for non-pregnant patient
- Despite limited data on safety and long-term use of fluoroquinolones in pregnancy, they are considered the drug of choice for MDR-TB treatment during pregnancy
- Treatment should be done through a multi-disciplinary approach and the management must be done in full collaboration of the Obstetrician.
- Avoid multiple X-rays. Treatment monitoring should be focused on clinical picture and smear results.
- The safety of the BPal regimen in pregnant and lactating women has not been established.
- Levofloxacin is included in Hr-TB regimens except in the following instances: when rifampicin resistance cannot be tested for, when there is documented resistance or known intolerance to fluoroquinolones, and when there is pre-existing prolongation of the QT interval and pregnancy. If a fluoroquinolone cannot be used, a patient with Hr-TB can still be treated with 6(H)REZ.east feeding:

A breastfeeding mother with active DR-TB should receive timely full course of anti-TB treatment to prevent disease transmission to the baby.

- Positive sputum smear mother should not take care of her baby until become smear negative if possible. The care of the infant should be done by the other family members.
- If the mother is on effective treatment, the mother and infant may spend time together, in a well ventilated area or outdoors.
- The mother should wear a surgical mask during breastfeeding.
- Formula milk may also be considered.

Contraception

Birth control is strongly recommended for all non-pregnant sexually active women receiving therapy for drug-resistant TB because of the potential consequences for both the mother and fetus resulting from drug-resistant TB treatment during pregnancy.

There is no contraindication to the use of oral contraceptives. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy.

These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-TB treatment medications. Patients who vomit at any time directly after, or within the first two hours after taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets being tolerated.

For patients with mono- and poly-resistant TB but who are susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options following consultation with a physician: (i) the use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or (ii) the use of another form of contraception.

Condoms are a reasonable solution for patients who do not want to take additional pills and/or when protection against sexually transmitted diseases is also needed. Patients should be aware that condom use is not as effective as contraceptive pills, especially when not used correctly. Medroxyprogesterone intramuscular injections and other methods of contraception can also be considered.

Children

Majority of children have been infected through contact with adults having DR-TB. Because of inability to produce sputum and their paucibacillary nature, it is difficult to perform DST in children. The culture negative DR-TB close contacts children with clinical evidence of active TB, the selection of treatment must be guided from DST result of source case and source's case history of TB drug exposure. Children can be given all second line drugs however, injectable must only be used when all oral drugs cannot be used due to DST pattern or previous drug exposure of source case. In case, use of injectable is imminent, the susceptibility on DST must be established and facility to monitor hearing loss must also be ensured.

As per new WHO recommendations, Bedaquiline and Delamanid are safe to be used in children. The use of Bedaquiline in adults >18 years is strongly recommended however; it may also be used in patients aged 6-17 years. Similarly, Delamanid is also safe to be used in children from age >3 years.

Other drugs like fluoroquinolone, Cycloserine, Ethionamide and PAS have been used effectively and are well tolerated in children. Treatment failure should be suspected in patients with weight loss, failure to thrive & worsening clinical conditions.

Pediatric formulations of most drugs are also available.

Diabetes Mellitus

The risk of poor outcomes increases manifold in patients with diabetes. Diabetes also potentiates TB drugs side effects e.g. renal insufficiency & peripheral neuropathy. DM need to be closely managed, although oral hypoglycemic agents or insulin are not contraindicated but may require increased dosages. Use of Eto/Pto may impair control of insulin levels. Serum creatinine and potassium should be closely monitored in patients with diabetes.

The management of a diabetic DR-TB patient must be done by a multi-disciplinary team with the inclusion of an endocrinologist or a medical specialist. Records of Meetings must be kept in the patient file for reference.

Renal Insufficiency:

Care should be taken in the administration of second-line drugs in patients with renal insufficiency while the dose and/or the interval between dosing should be adjusted as per table below.

Table 25 Adjustment of anti TB drugs due to renal insufficiency

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis
INH	No change	300 mg once daily, or 900 mg three times per week
R	No change	600 mg once daily, or 600 mg three times per week
Z	Yes	25–35 mg/kg per dose three times per week (not daily)

E	Yes	15–25 mg/kg per dose three times per week (not daily)
Lfx	Yes	750–1000 mg per dose three times per week (not daily)
Mfx	No change	400 mg once daily
Cs	Yes	250 mg once daily, or 500 mg/dose three times per week
Eto	No change	250–500 mg per dose daily
PAS	No change	4 g/dose, twice daily
Am	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Lzd	No	600 mg daily
Cfz	No	200-300 mg daily in first 2 months followed by 100 mg daily
Bdq	No	400 mg once daily for 2 weeks, then 200 mg three times per week
Dlm	No	100 mg twice daily
Imm/Cls	Yes	For creatinine clearance 20-40 ml/min -500 mg every 8 hours For creatinine clearance <20 ml/min - 500 mg every 12 hours.
Mpm	Yes	For creatinine clearance 20-40 ml/min -500 mg every 8 hours For creatinine clearance <20 ml/min - 500 mg every 12 hours.

Table 26 Example of calculating creatinine clearance

Est GFR (creatinine clearance) = Weight (kg) x (140 – age) x (constant)/ Serum creatinine (µmol/L)

The constant in the formula = 1.23 for men and 1.04 for women. The creatinine is measured in the serum of the blood.

Normal values for creatinine are:
For women: 45-90 µmol/L (about 0.5 to 1.0 mg/dl)
For men: 60-110 µmol/L (about 0.7 to 1.2 mg/dl)
If creatinine is reported in conventional units (mg/dl) from the laboratory, one can convert it to a SI Unit (µmol/L) by multiplying by 88.4.
(For example a creatinine = 1.2 mg/dl is equivalent to (88.4 x 1.2) = 106.1 µmol/L.)
Weight should be entered in the formula as the ideal body weight and is calculated with the following formula:
Ideal body weight (men) = 50 kg + 1 kg/cm height over 150 cm.
Ideal body weight (women) = 45 kg + 1 kg/cm height over 150 cm.

Normal values for the creatinine clearance are:
Women: 88 to 128 ml/min
Men: 97 to 137 ml/min
Example: A female patient has a serum creatinine = 212 µmol/L, age = 46, ideal body weight = 50 kg.

What is the creatinine clearance?

Calculate the creatinine clearance:
Weight (kg) x (140 – age) x (constant) / Serum Creatinine =
50 x (140 – 46) x (1.04 for women)/ 212 = 23.0 ml/min

The creatinine clearance is below 30, refer to relevant Table and every drug in the regimen should be examined and adjusted if necessary accordingly

Note: Creatinine clearance can also be calculated with a 24-hour urine and the serum creatinine, but this is usually more cumbersome.

Liver Disorders:

Pyrazinamide should not be used in patients with chronic liver disorder. Close monitoring of liver enzymes to detect any abnormality while stopping the offending drug.

In case of unrelated acute hepatic injury, clinical judgment is needed to either continue to halt treatment till the liver injury resolves. The anti TB treatment may be deferred until hepatic injury subsides or maybe started with combination of four non-hepatotoxic drugs as the safest option.

Due to high frequency of hepatitis viral infection in the country, testing must be done to assess status at baseline and dosing modification if needed.

Seizures:

In patients with known history of seizures it is advisable to evaluate whether the patient is on anti-seizure medication and if the seizures are controllable or not. In case of uncontrollable seizure, it is advisable to treat underlying causes with anti-seizure medication before start of MDR treatment. Cycloserine should be avoided in patients with uncontrollable seizure. In case where addition is inevitable, anti-seizure medications should be adjusted to control the seizure.

- If Short term regimen is used: It should be kept in mind that Isoniazid interacts with anti-seizure medications
- For DR-TB with rifampicin sensitivity: It should be kept in mind that rifampicin interacts with anti-seizure medications

Drug interactions should be checked before use.

Psychiatric disorder:

Any existing psychiatric disorder must be evaluated and a properly addressed to establish comparison with new ones during treatment. There is higher incidence of depression with MDR TB treatment especially associated with chronicity and lower socioeconomic status.

Although use of Cycloserine augments such disorders but due to higher benefits to risk ratio is not absolutely contraindicated. Close monitoring is needed in such patients to timely identify any signs of psychiatric illness and be amply managed.

Substance abuse

Patients with substance abuse should be managed for their addiction. Complete abstinence is strongly encouraged however; active consumption is not contraindicated for MDR treatment. In case of interruption due to substance abuse, suspend MDR treatment until complete treatment of addiction.

Section 7:

MDR-TB and HIV Co-infection:

Collaborate activities for TB HIV Control:

Activities needed in areas with DR-TB treatment in order to decrease burden of HIV-TB are as follows:

- Establishment of mechanism for collaboration: Coordinating body at National & Provincial level with availability of HIV expert, HIV surveillance of TB patients, joint TB-HIV planning and monitoring and evaluation
- Decreasing TB in people with HIV: three I's: intensified case finding, Isoniazid preventive therapy (IPT), Infection control in health care setting
- Decreasing HIV in TB patients: provision of HIV counselling & testing, HIV preventative methods, introduction of Cotrimoxazole preventive therapy (CPT) and anti-retroviral therapy (ART) and provision of HIV care & support

The following set of activities will be implemented:

- Determining prevalence of TB drug resistance in HIV population
- Routine HIV testing in all RR/MDR patients
- XPert/Rif testing for co-infected patients to diagnose smear negative patients and screening for MDR
- Culture for sputum and other tissues to diagnosis smear negative patients
- DST at start of TB therapy to identify RR/MDR TB
- Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm_3). Close treatment follow-up for side effects treatment, clinical management and prophylaxis of opportunistic infections and nutritional support
- Provision of Socioeconomic support
- TB infection control for early diagnosis and prompt initiation of treatment with separation and airborne infection control protocols implementation
- Continuous liaison with TB/HIV coordinating committee

Clinical features and diagnosis of MDT TB in HIV patients:

The clinical picture of DR-TB in HIV infection does not differ from that of drug susceptible TB. The diagnosis is difficult with majority presents as extra pulmonary & sputum smear negative. This may result in delays in diagnosis with high chance of mortality and morbidity. The use of X-rays, Xpert, molecular diagnosis and culture improves diagnosis.

Treatment of DR TB and HIV

ART initiation improves survival and slows progression to AIDS. If the patient is already on ART and diagnosed with DR-TB, evaluation (clinical, CD4 count, viral test loading) should be done to see if the ART is failing with a need for a new ART regimen. ART may cause adverse effects that may eventually halt both HIV and DR-TB treatment.

The following is needed to be considered in such scenarios:

Table 27 Issues regarding treatment of DR-TB with HIV infection:

Issue	Comment
Drug Interactions	1. It is not recommended to use Bedaquiline and Efavirenz in combination. 2.Rifampicins lower levels of some anti-viral drugs and contribute drug resistance (protease inhibitors and non-nucleoside reverse transcriptase inhibitors). 3.ARVs increase the level of Rifampicin and risk of toxicity 4.Non enteric coated didanosine when given together with FQs may decrease FQs absorption hence should not be given at the same time.
Drug toxicity	1. Peripheral neuropathy increased by aminoglycoside, stavudine, Cycloserine, pyrazinamide 2. GI effects with higher pill burden 3. Avoid use of injectable and tenofovir due to renal toxicity 4. Neuropsychiatric effects with Cs and efavirenz but these drugs can be used together
Immune reconstitution inflammatory syndrome (IRIS)	1.Worsening of patient's clinical status 2. Presents within 3 months of initiation of ART with low CD4 Count (<50 cells/mm3) 3. Manage with NSAIDs (mild disease) and steroids (severe disease) 4. No interruption of ART needed for management
Monitoring	1.ART must be included in DOT for MDR TB treatment 2. Same monitoring as HIV negative, creatinine and potassium monitoring every two week while on injectable 3. In case of treatment failure, ART and MDT regimen re-evaluation is needed
Infection control	1.Increased occurrence of DR-TB in HIV positive patients 2. Weak infection control increases the risk of MDR TB in HIV patients 3. Implementation of infection control at hospital is required

Section 8:

Management of Adverse Events

Side effects caused by second line anti TB drugs must be promptly identified and managed accordingly. For more details, see "A Handbook to implementation of National Guidelines on aDSM"

A. Pre-treatment Assessment:

A thorough baseline evaluation (medical history and physical examination) is done to identify patients who are increased at risk of adverse effects. Therefore, monitoring during the management of MDR-TB must be more intensive in patients with pre-existing conditions (diabetes mellitus, renal insufficiency, liver disease, thyroid disease, drug/alcohol abuse, mental illness, HIV infection, pregnancy, lactation and many others.

B. Monitoring for adverse effects during treatment:

Patients on second-line drugs are prone to experience adverse effects and need extensive closed monitoring. Directly observed treatment is preferable option over self-administration as Physician can recognize any new onset of adverse effects during the course of MDR-TB treatment. Although the patient may be the first spontaneous source of information for experiencing any untoward effect, it is important to have a systematic method of interviewing patients as they may feel reluctant in reporting or delay due to having adverse effects which are yet to become clinical.

The following common symptom must be regularly screened during DOT provision:

- Rashes
- GI symptoms (nausea, vomiting, diarrhea)
- Psychiatric symptoms (psychosis, depression, anxiety, suicidal tendency)
- Jaundice
- Ototoxicity
- Peripheral neuropathy
- Electrolyte wasting (muscle cramping, palpitations)
- Cardiac rhythm abnormality

Table 28 Following grading criteria maybe used to estimate severity of adverse effects (DMID 2007)

Grade-1	Mild Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
Grade-2	Moderate Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
Grade-3	Severe Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
Grade-4	Life-threatening Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

C. National active TB Drug Safety Monitoring and Management (aDSM):

The National TB Program introduced STR (2018) and new TB drugs, Bedaquiline (Bdq) and Delamanid (Dlm) for the treatment of MDR-TB (& XDR-TB) in 2016. With the increased use of the new drugs and new regimens, the establishment and implementation of a national system on active TB drug-safety monitoring and management (aDSM) are necessary when the safety profiles of TB drugs and regimens are unknown. The national aDSM system is important to ensure patient safety and contribute to the policy development for the new TB drugs and regimens.

The term 'active TB drug-safety monitoring and management' (aDSM) defines active and systematic clinical and laboratory assessment of patients while on treatment. aDSM applies to patients on treatment with: (i) new anti-TB drugs; (ii) novel DR-TB regimens; or (iii) extensively drug-resistant TB (XDR-TB) regimens, in order to detect, manage and report suspected or confirmed drug toxicities. The core component for such a strategy is to record and report serious adverse events (SAEs) while in the light of availability of additional

resources may expand monitoring of other AEs of clinical and special significance to the PMDT program. All serious adverse events should be reported by PMDT staff using the "Serious Adverse Event Reporting Form" within 24 hours of identification by email to provincial and national MDR-TB Units. Implementation, management and supervision necessary for aDSM must be integrated into existing PMDT component of continuous patient care and monitoring.

The main objectives of aDSM are to reduce risks in patients on SLDs treatment for DR-TB, create a drug safety profile for new drugs regimens and to change the policy whenever required. aDSM includes three essential activities to achieve these objectives:

1. Active and systematic clinical and laboratory investigation to detect AEs and toxicity.
2. Timely management of AEs to deliver best possible patient care
3. Systematic collection, reporting & analysis of data to assess the types of SAEs, assess the safety of treatment and impact development in future policy

D. Management of adverse effects:

Mild adverse reactions may be managed with the help of ancillary drugs while the patient can be continued on current regimen.

Some adverse events may diminish by the passage of time and need active intervention. Decreasing dose of a particular drug may be an option in a case a potential causative agent is identified. However, lowering it below a certain level where adequate serum level is not achieved may also render the regimen ineffective.

Pyridoxine (Vit B6) should be given to patients on high dose Isoniazid and may be given to patient on, Cycloserine or Terizidone to protect against neurological adverse effects. Oral magnesium can be used in patients with hypokalemia.

It is important to remember that an MDR regimen is the most effective and one of the last option to efficiently cure a patient. Hence, development of new strains of bacteria as a result of non-adherence and non-compliance, the patient may have to be shifted onto a less effective and more toxic regimen.

Some of the most common and life threating toxicities are as follows:

- **Nephrotoxicity:** it is a common adverse effect caused by second line injectable drugs both aminoglycoside (amikacin, kanamycin, streptomycin)
- **Electrolyte wasting:** Loss of electrolytes is a common complication of the anti-TB injectable drugs, most frequent with aminoglycosides. Although it ensues late in the treatment cycle but is reversible once offending agent is stopped. In order to detect of any imbalance serum potassium should be checked at least monthly in all patients while they receive an injectable agent.
- **Hypothyroidism:** Hypothyroidism is commonly caused by PAS and/or Ethionamide/prothionamide and confirmed by serum TSH testing following clinical assessment. The patients must be screened for hypothyroidism with a serum TSH every 3 months for the first 6 months, and then every 6 months thereafter. Screening with TSH should occur sooner if symptoms of hypothyroidism arise. The dosing of thyroid replacement therapy should be guided using serum levels of TSH every month until a stable dose of thyroid replacement hormone is reached. Goiters can develop due to the toxic effects of PAS, Ethionamide and/or prothionamide. In areas with endemic iodine deficiency goiters, treatment with iodine is also indicated.
- **Liver toxicity:** Damage to liver can result from pyrazinamide, PAS and with the other second-line anti-TB drugs. Liver enzymes should be checked for all patients who exhibit signs of hepatotoxicity.
- **Ototoxicity:** Ototoxicity usually manifests by hearing loss, tinnitus (ringing in the ear), and/or other vestibular symptoms, such as nystagmus, ataxia, and disequilibrium. It most commonly occurs in patients on aminoglycosides. The ototoxic effects maybe aggravated by simultaneous use of furosemide. Patients starting therapy with hearing loss at baseline from prior aminoglycoside use should not start it. Hearing loss is generally not reversible upon discontinuation of therapy. Audiometry for baseline and/or follow-up testing is required to pick up early hearing loss. It is recommended to do audiometry monthly while on the injectable agent. If any hearing loss is detected (including Grade-1), stop the injectable agent. Decreasing dosing frequency to three times weekly with close monitoring (weekly audiometry) is preferred in cases where replacement to injectable is not possible.

- **Psychiatric disturbances:** Suicidal tendencies can result from DR-TB treatment in addition to other manifestation e.g. psychosis and depression. Detailed psychosocial assessment with specific questions like "Are you having thoughts of suicide?" should be done routinely at the monthly visit. Other signs of psychosis, anxiety, agitation and depression should also be assessed during the monthly follow up.

Table 29 Common Side effects, suspected agents and management strategies

Adverse Effects	Suspected Agents	Management strategies	Comments
Rash, allergic reaction and anaphylaxis	Any drug	1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be used with continuation of the medication. They include: • Antihistamines • Hydrocortisone cream for localized rash • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful. • Photo toxicity may respond to sunscreens, but these can also cause rash • Dry skin may cause itching (especially in diabetics); liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with Clofazimine 4. Once rash resolves, reintroduce remaining drugs one at a time, with the most likely culprit last. Consider not re-introducing in the challenge any drug that is highly likely to be the culprit. 5. Permanently suspend any drug identified as the main cause of a serious reaction.	1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flashes, itching, palpitations can be caused with isoniazid and tyramine-containing foods (cheese, red wine). If this occurs advise patients to avoid foods that precipitate the reaction. 3. Hives (urticaria) can be caused by any drug. To identify the drug, introduce the drugs one at a time. In the case of hives, a desensitization attempt can be made. 4. Any drug that resulted in anaphylaxis or Steven-Johnson syndrome should never be reintroduced to the patient, not even as a challenge.
Nausea And vomiting	**Eto, Pto, PAS,** H, E, Z, Cfz, Bdq, Dlm	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis; initiate rehydration therapy and correct any electrolyte disturbances. Check hemoglobin (hematemesis) and treat possible bleeding ulcers. 2. Initiate stepwise approach to nausea and vomiting.	1. Nausea and vomiting is common in early weeks of therapy and usually decreases with time and adjunctive therapy. The patient may need to tolerate specifically in the initial treatment period. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give IV fluids and

		Phase 1: Adjust medications and conditions without lowering overall dose: • Give the Eto/Pto at night • Give Eto or PAS twice or thrice daily. • Give a light snack (biscuits, bread, rice, tea) before the medications. • Give PAS 2 hours after other anti-TB drugs **Phase 2:** Start antiemetic(s): • Metoclopramide 10 mg 30 minutes before anti-TB medications. • Ondansetron 8 mg 30 minutes before the anti-TB drugs and again 8 hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used) For refractory nausea 24 mg 30 minutes before the dose can be tried. **Phase 3:** Decrease dose of the suspected drug by one weight class if this can be done without compromising regimen. Rarely is it necessary to suspend the drug completely.	replace electrolytes as needed. 3. Another strategy is to stop a responsible medicine for two or three days and then add it back, gradually increasing the dose (advice the patient the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated). 4. Ondansetron is serotonin 5-HT3 receptor antagonist is a strong anti-emetic? Other anti-emetics from this class of serotonin 5-HT3 receptor antagonists exist. Trying different anti-emetics, may also be proven helpful. 5. For some patients particularly anxious about the nausea, a small dose of an anti-anxiety medicine (5 mg of diazepam) 30 minutes prior to the anti-TB drugs can help.

Adverse Effects	Suspected Agents	Management strategies	Comments
Gastritis & abdominal pain	**PAS, Eto, ,Cfz,** FQs, H, E, and Z	1. Abdominal pain can also be associated with serious adverse effects such as pancreatitis, lactic acidosis, and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend suspected agent. 2. If symptoms are consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux), initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid the use of antacids as they decrease absorption of FQs. 3. For severe abdominal pain, stop suspected agent(s) for short periods of time (one to seven days). 4. Lower dose of suspected agent, if this can be done without compromising regimen. 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Severe gastritis, as manifested by blood in the vomit or stool, is relatively rare. 2. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of the FQs (take 2 hours before or 3 hours after anti-TB drugs). 3. Stop any NSAIDs drugs 4. Diagnose and treat H-pylori infections. 5. Severe abdominal distress and surgical abdomen have been reported with the use of Clofazimine. Although these reports are rare, if this effect occurs, Clofazimine should be suspended.

Adverse Effects	Suspected Agents	Management strategies	Comments
Diarrhea and/or flatulence	**PAS,** Eto	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhea is severe. 5. Fever and diarrhea and/or blood in the stools indicate the diarrhea may be secondary to something other than a simple adverse effect of the anti-TB drugs	1. Consider other causes of diarrhea: • Pseudo-membranous colitis related to broad-spectrum antibiotics such as the FQs is a serious and even life-threatening condition. Fever, bloody diarrhea, intense abdominal pain and increased white blood cells are danger signs of possible pseudomembranous colitis. • Parasites and common water-borne pathogens in the area should be looked for in the patient and treated if present. • Lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet. 2. Loperamide can be used in children over 2 years old.

Adverse Effects	Suspected Agents	Management strategies	Comments
Hepatitis	**Z, H, R, Eto,** and PAS, Bdq	1. If enzymes are more than three times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three nonhepatotoxic medications (an example of three non-hepatotoxic drugs are the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, stop all drugs. 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the two most common causes) and treat any identified. 3. Consider suspending most likely agent permanently. Reintroduce remaining drugs one at a time, with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely culprit is not essential, consider not re-introducing it.	1. History of previous drug hepatitis should be carefully analyzed to determine most likely causative agent(s); these drugs should be avoided in future regimens. 2. Viral serology should be done to rule out other etiologies of the hepatitis if available, especially to A, B, and C. 3. Alcohol use should be investigated and alcoholism addressed if found. 4. Generally, hepatitis due to medications resolves upon discontinuation of suspected drug.

Adverse Effects	Suspected Agents	Management strategies	Comments
Hypothyroidism	**Eto, PAS**	1. Most adults will require 100 to 150 mcg of levothyroxine daily. Start levothyroxine in the following manner: • Young healthy adults can be started on 75 to 100 mcg daily • Older patients should begin treatment with 50 mcg daily • Patients with significant cardiovascular disease should start at 25 mcg daily. 2. Monitor TSH every 1 to 2 months and increase dose by 12.5–25 mcg until TSH normalizes. Adjust dose more slowly in the elderly and patients with cardiac conditions.	1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate. 2. Do not start treatment unless TSH is above 1.5 to 2.0 times upper normal limit. 3. Completely reversible upon discontinuation of PAS and/or Ethionamide/prothionamide . 4. The combination of Ethionamide / prothionamide with PAS is more frequently associated with hypothyroidism than is the individual use of each drug.

Adverse Effects	Suspected Agents	Management strategies	Comments
Arthralgia	**Z,** FQs, Bdq	1. Initiate therapy with non-steroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400–800 mg three times a day). 2. Lower dose of suspected agent (most commonly pyrazinamide), if this can be done without compromising regimen. 3. Discontinue suspected agent, if this can be done without compromising regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgia, although if gout is present it should be used. 3. If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (gout, infection, autoimmune disease, etc.).
Tendonitis and tendon		1. If significant inflammation of tendons or tendon sheaths occur:	1. Tendon rupture with FQ use is more likely in

rupture		• Consider stopping FQs • Give an NSAID (ibuprofen 400 mg four times daily) • Rest the joint 2. If treatment failure is likely without the fluoroquinolone • Reduce dose if possible • Strict resting of the joint • Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the FQ.	patients doing new physical activities and more common in older patients and diabetics. 2. Tendon rupture is relatively rare.
Electrolyte disturbances (hypokalemia and hypomagnesaemia)	**Am, S**	1. Check potassium. 2. If potassium is low, also check magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from FQ as they can interfere with FQ absorption.	1. If severe hypokalemia is present, consider hospitalization. 2. Amiloride 5–10 mg per day or spironolactone 25 mg per day may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhea.
Nephrotoxicity (Renal toxicity)	**S,,** **Am,**	1. Discontinue suspected agent. 2. Consider other contributing etiologies (NSAIDs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated. 3. Follow creatinine (and electrolytes) closely, every 1 to 2 weeks. 4. Consider dosing the injectable agent at 2-3 times a week if the drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite 2-3 times a week dosing, suspend the injectable agent. 5. Adjust all TB medications according to the creatinine clearance	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2. An example of how to calculate a creatinine clearance based on the serum creatinine is provided. 3. Renal impairment may be permanent.
Vestibular Toxicity (tinnitus and	**S, ,** **Am,** **,** Cs, FQs, H	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to 2 or 3 times a week.	1. Ask the patient monthly about tinnitus and unsteadiness.

dizziness)	Eto, Lzd, Dlm (dizziness)	2. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. **This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents.**	2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity. 3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, INH or Linezolid. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve with withholding medications.
Hearing loss (also see vestibular toxicity above)	**S, ,** **Am,,**	1. Document hearing loss and compare with baseline audiometry if available. (Some degree of hearing loss occurs with most patients, starting with high-frequency loss). 2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to 2 or 3 times a week. 3. Discontinue the injectable agent if this can be done without compromising the regimen.	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of DR-TB therapy. 2. Hearing loss may be reversible or permanent (often permanent). 3. Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. This should be discussed between a physician trained in DR-TB and the patient. **Continuing the injectable agent despite hearing loss almost always results in deafness.** 4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial

			use to determine if a patient with hearing loss can benefit from their use.
Peripheral neuropathy	**Cs, Lzd, H, S, , H,** Fluoroquinolones, rarely Eto, E, Dlm (parestesias)	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. (Lowering the dose of likely culprits can also be done – linezolid, isoniazid, Ethionamide). 3. Initiate medical therapy: • NSAIDs or acetaminophen may help alleviate symptoms. • Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime; the dose may be increased to a maximum of 150 mg). Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors (SSRIs) anti-depressant drugs. • Carbamazepine, an anticonvulsant, at 100–400 mg twice daily can be tried. 4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.	1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible but many patients experience improvement when offending agents are suspended. However, the neuropathy associated with linezolid is common after prolonged use and often permanent (for this reason suspension of this agent should be considered when neuropathy develops).
Depression	**Socioeconomic circumstances, chronic disease, Cs,** fluoroquinolones, H, Eto, Dlm (anxiety)	1. Assess and address underlying socioeconomic issues. 2. Assess patients for co-existing substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is smear- and culture-negative). 4. When depression is more significant, initiate antidepressant therapy (amitriptyline, fluoxetine or similar). Tricyclic antidepressants and SSRIs should be given together and should not be given to patients on linezolid. 5. Lower dose of suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and Ethionamide to 500 mg daily to see if the depression is lessened is a common strategy).	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment. If significant depression

		6. Discontinue suspected agent if this can be done without compromising regimen.	is present at the start of treatment, avoid a regimen with cycloserine if possible. 4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.
Suicidal ideation	**Cs,** H, Eto	1. Hospitalize the patient and put under 24-hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and/ or Eto/Pto.
Psychotic Symptoms	**Cs, H,** FQs	1. Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high-dose isoniazid. 2. If moderate to severe, initiate antipsychotic therapy (haloperidol). 3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others. 4. Increase pyridoxine to maximum daily dose (200 mg per day). 5. Lower dose of suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising regimen. 6. Discontinue suspected agent if this can be done without compromising regimen. 7. Once all symptoms resolve and patient is off cycloserine, anti-psychotic therapy can be tapered. If cycloserine is continued at a lower dose, anti-psychotic therapy may need to be continued and any attempts at tapering should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs.	1. Some patients will need to continue antipsychotic treatment throughout DR-TB therapy (and discontinue upon completion of DR-TB therapy). 2. Previous history of psychiatric disease is not a contraindication to the use of cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. 3. Some patients will tolerate cycloserine with an antipsychotic drug, but this should be done in consultation with a psychiatrist as these patients will need special observation and this should only be done when there is no other alternative. 4. Psychotic symptoms are

			generally reversible upon completion of DR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new-onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.
Seizures	**Cs, H, fluoroquinolones**	1. Hold cycloserine, FQs and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin, or valproic acid are most commonly used). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium (K+), sodium (Na+), bicarbonate (HCO3−), calcium (Ca2+), magnesium (Mg2+), chloride (Cl−). 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.	1. Anticonvulsant is generally continued until DR-TB treatment is completed or suspected agent discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available). 3. Patients with history of previous seizures may be at increased risk for development of seizures during DR-TB therapy. 5. Always check creatinine in patients with new-onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of

			cycloserine in the presence of low creatinine may be all that is needed to control the seizures.
Optic neuritis	**E,** Eto, Lzd, Cfz, rifabutin, H, S	1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist.	1. The most common drug responsible is ethambutol. 2. Usually reverses with cessation of ethambutol. 3. Improve diabetic control in diabetic patients.
Metallic Taste	**Eto**, FQs	1. Encourage the patient to tolerate this side effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gynecomastia	**Eto**	1. Breast enlargement can be a troublesome side-effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported. 2. Encourage patients to tolerate this side effect.	1. Resolution occurs after treatment is stopped.
Alopecia	**H, Eto**	1. Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment. 2. Encourage patients to tolerate this side effect.	1. Significant cosmetic change has not been reported.
Superficial fungal infection and thrush	**FQs** and other antibiotics	1. Topical antifungal agents or short-course oral antifungal drugs are helpful. 2. Exclude other diseases if response to treatment is not prompt (such as HIV).	1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Lactic Acidosis		1. Stop linezolid if lactic acidosis occurs. Symptoms: abdominal pain, nausea, vomiting, rapid deep breathing, general weakness.	1. Lactic acidosis can be monitored with a blood test to measure lactic acid.
Dysglycaemia	Eto, Lzd	2. Treat diabetes as needed. Good glucose control is important during treatment.	1. Lzd may cause hypoglycemia in patients on oral hypoglycemic drugs or insulin.
QT prolongation	FQs (Mfx more than Lfx), Bdq, Dlm, Cfz	1. Values of QT greater than 450 ms should cause concern. For any patient found to have a value greater than 450 ms: • Strictly keep electrolytes within normal range, monitoring every two weeks. (It is	1. QT prolongation is characteristic of the entire FQ class. Of the currently available agents,

		suggested to maintain potassium levels of more than 4 mEq/L and magnesium levels of more than 1.8 mg/dL) • Avoid other drugs that increase the QT intervals. • Monitor the patient's renal and hepatic and adjust dose of fluorquinolones if impairment is present. 2. Consider suspension of the FQ if risk of torsades de pointes outweighs the benefits of the drug. (management of QT prolongation is given at **Annex)**	moxifloxacin causes the greatest QT prolongation and levofloxacin and ofloxacin have a low risk of QT prolongation. 2. Patients who experience a prolonged QTc interval are at risk for developing torsade de pointes (torsades). Torsades is a life threatening arrhythmia, but not every patient who has a prolonged QTc develops torsades.
Hematological Abnormalities	**Linezolid**	1. Stop linezolid if Myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. 2. Consider blood transfusion for severe anemia.	1. Hematological abnormalities (leukopaenia, thrombocytopenia, anemia, red cell aplasia, coagulation abnormalities, and eosinophilia) can rarely occur with a number of other anti-TB drugs. 2. There is little experience with prolonged use of liniezolid.

Table 30 Management of prolongation of QT interval

QTcF on ECG at baseline	Action
<450 ms = normal	Start BDQ/ and repeat ECG after 2 weeks **(not eligible for BDQ if baseline QTcF>450ms- Consult expert)**
QTcF on follow-up ECG done monthly	**Action**
<450 ms = normal	Cont BDQ with routine QTcF monitoring
450-469 ms or increase in interval <30 msec = mild prolongation	Cont BDQ with routine QTcF monitoring
470-499 ms or increase in interval 30-50 msec = moderate prolongation	If no clinical cardiac symptoms (chest pain, palpitations, dizziness and syncope) then continue BDQ and repeat ECG after **1 week** If clinical cardiac symptoms then withhold QT prolonging drugs (described below) and repeat ECG within 1 week

Presenting QTc>500 ms during follow up Or increase in interval >50 msec = severe prolongation	Repeat ECG after 30 mins If prolongation persists, check potassium levels and if possible check calcium and magnesium levels. Test renal/hepatic functions and TSH. **Actions to be taken:** Replace potassium and magnesium. Suspend all QTC prolongation agents including ancillary medications. First discontinue drugs with shortest half-life (usually FQ or DLM) followed by CFZ, then BDQ. Cardiologist referral. If symptomatic with palpitations, arrhythmia or syncope, consider hospital admission for close monitoring. If TdP is identified, management should be in hospital with magnesium infusion and ideally with access to phasing pacemaker and defibrillator. Consider alternative DRTB regime and closely monitor the patient throughout the treatment cycle. Once stable (QTcF<500 and normal electrolytes), critical QTc prolonging drugs maybe added if needed. In case of MFX related QTc prolongation consider high dose Lfx as a safer alternative.

Table 31 Commonly used ancillary drugs

Indication	Drug
Nausea, vomiting, upset	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of FQ
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity Reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids

	(dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

Table 32 Role of specialists (where available) in management of side-effects and/or any other complications

Side Effect	Referral to specialist
• Difficult to control with Oral Hypoglycaemic Agent • Brittle diabetes • Problems of hypo-/hyperglycemia • Thyroid problems	Endocrinologist
• Treatment complications with underlying liver disease like Hepatitis B/C infection • Cirrhosis of liver	Hepatologist
• Complication of hematemesis and melena	Gastroenterologist
• Severe psychiatric problems, e.g. severe depression, anxiety or neurosis • Major psychiatric disorders, e.g. schizophrenia or new onset psychosis	Psychiatrist
• Progressive renal impairment • Severe enough for renal replacement therapy	Nephrologist
• Unexpected complications, e.g. severe dermatitis not relieved from withdrawal of likely causal drugs and not responding to routine anti-allergic agents and treatment	Dermatologist

Section 9:

Treatment of Isoniazid Resistant TB (Hr-TB)

Who may be considered for investigation for Isoniazid Resistance treatment (Hr-TB)

In Pakistan INH resistance is investigated in TB patients who are on FLD treatment with 2RHZE /4RH, and have positive smear at 2 months. According to NTP protocol, Xpert testing should be repeated for RR and if rifampicin resistance is not detected on repeat testing, the patient should be investigated for INH resistance and FQ resistance preferable using FL and SL LPA.

Treatment regimen for Hr-TB:

· If rapid DST is available and LPA shows Rif sensitive, INH resistant and Lfx sensitive, the treatment may be modified and patient may be started on 6RHZE+Lfx, in line with WHO recommendations.

· If rapid DST is available and LPA shows Rif sensitive, INH resistant and Lfx resistant, the treatment should continue with 6RHZE.

· Any situation where rapid DST is not feasible due to accessibility (from health facility to LPA laboratory) and considerable delay in LPA result (months) are anticipated, treatment with 6RHZE should be continued for six month. (NTP recommended regimen for FQ resistance associated with INH resistance)

Concerns regarding Treatment of Hr-TB

One concern regarding changing to an FQ-containing regimen is that rifampicin resistance may be missed by the routine test used. GeneXpert misses up to 8% Rif resistant cases (with other mutations). Clinical assessment of the patient for the possibility of Rif's resistance is important and in cases of potential risk, referral for Rif resistance testing by phenotypic DST or sequencing needs consideration.

Furthermore in our population, up to 13% of the RR are missed on phenotypic DST (MGIT), although it is of the lesser concern in program setting where Xpert is used as an initial test for the detection of RR. However, for any TB patient with INH resistance detected on phenotypic DST in rifampicin sensitive isolates should be tested on Xpert (to rule out Rifampicin resistance) before any decision for treatment for Hr-TB. Prescribing Lfx containing regimen to any patients with occult RR carries a risk of rapidly developing Lfx-resistance since both Inh and Rif are ineffective, making subsequent treatment for RR-TB more difficult

Section 10:

Infection Prevention & Control

Tuberculosis spreads through the air from an infectious TB patient (who has not been on proper anti TB treatment) to another person. The three factors which increases the risk of transmission are

- Infectiousness of patient (smear positive, cavitation, severity of cough)
- Inappropriate or unsupervised treatment
- Co-existing medical factors in the person being infected (DM, HIV, malnutrition, children)

The transmission depends on:

- The number of bacilli produced by the patient.
- The number of persons in the exposed area (poor circulation of air).
- The degree of ventilation in the exposed area.
- The duration of exposure.

Following are the infection control measures that needs to be implemented at a health care setting and at home.

Table 33 Infection Control Measures

<table>
<tr><th>Sr.</th><th>Measures</th><th>Priority</th><th>Objective</th></tr>
<tr><td>1</td><td>Administrative control</td><td>First priority</td><td>Reduce exposure of all people within the area where there may be exposure to TB.</td></tr>
<tr><td colspan="4">The most effective but costly and difficult to apply. Respiratory control measures are less effective and useful without having administrative measures.

<u>In health care settings</u>:
•Rapid diagnosis of each person with TB.
•Separation and triaging of patients with cough.
•Outdoor collection of sputum samples in an isolated place at all times.
•Rapid initiation of effective treatment.
•Evaluation of the risk of transmission in health care facilities.
•Sensitization of staff, patients and their families, visitors.
•Monitoring for TB among health care workers involved in TB care.

<u>At home:</u>
•Simple measures:
··The patient should use a handkerchief when coughing.
··Open windows, ensure good ventilation of bedrooms.
•When the patient under treatment no longer has a cough, no special precautions are required.
•Do not provide unhelpful advice such as: separation of cutlery and eating utensils, isolation.</td></tr>
<tr><td>2</td><td>Environmental Control measures</td><td>Second priority</td><td>Reduce concentration of infectious particles.</td></tr>
<tr><td colspan="4"><u>Natural Ventilation:</u>
• Open doors and windows to maximize natural ventilation.
• Risk of infection with natural ventilation may be lower than with a poorly maintained mechanical ventilation system.
• Structures with high roofs and ceilings and large windows provide better natural ventilation than those with low roofs and ceilings and small or no windows.
• Lower maintenance costs.</td></tr>
</table>

<table>
<tr><td colspan="4">• Adequate in tropical regions.

<u>Mechanical ventilation</u>
• Ceiling and exhaust fans to increase the amount of ventilation
• UV lamps: Product lifetime: 7–14 months (10,000 hours); to be wiped every month with 70° alcohol</td></tr>
<tr><td>3</td><td>Individual respiratory protection</td><td>Third priority</td><td>Protect health personnel in areas where the concentration of particles cannot be reduced.</td></tr>
<tr><td colspan="4"><u>Surgical face masks:</u> prevent the passage of the wearer’s germs to others but do not protect the wearer from the germs of others.

<u>N95 respirators</u> are the last line of defense for health workers against nosocomial transmission. Without administrative and environmental control measures, respirators do not adequately protect health workers. They may be re-used several times if they are properly maintained. The most frequent causes of deterioration are humidity, dust and poor handling.</td></tr>
</table>

Reference: *FIELD GUIDE FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS-2018- The Union*

Section 11:

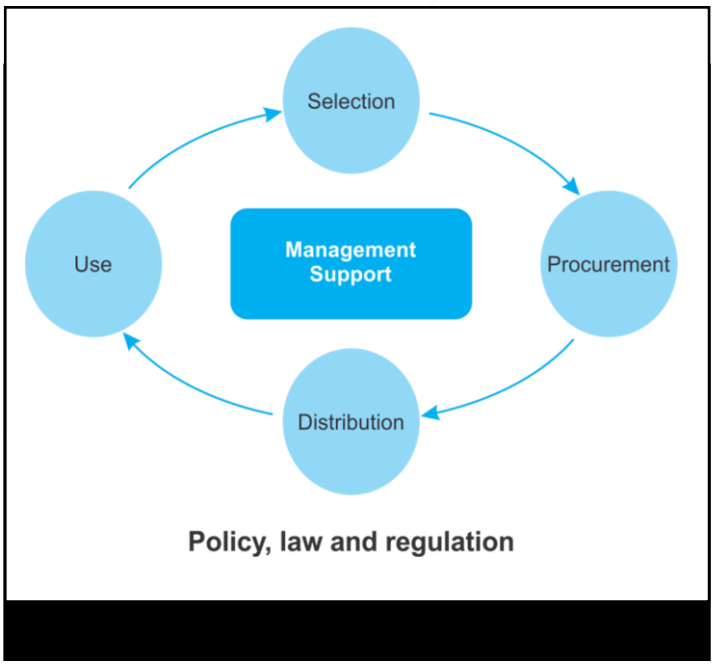
Procurement and Supply Chain Management

Procurement and Supply Chain Management (PSCM) is one of the backbones of national health programs ensuring the uninterrupted availability of quality health supplies, from the national level through to the Service Delivery Points (SDP) in rural and in the remotest areas of the country. High volume, around 55-60%, of the funds are budgeted for the procurement of Pharmaceuticals, Health and Non Health Products. PSCM capacity and activities (Human Resource, Processes and infrastructure, are few of the important ones) are critical to grant implementation and performance. Persistent challenges and associated risks related to PSCM functions directly affects the PSCM first and ultimately impacts the grant implementation as a whole.

PSCM is a set of practices through which Drug requirements are *quantified, procured and distributed* all the way from supplier to the ultimate user ensuring the availability of *right product, right quality, in right quantity, at right time, on right cost, to the right patient*. Following step-wise Drug Management activities define the above activities:-

Selection

The selection of medicines, is based on the treatment strategy provided in the National Guidelines for the Programmatic Management of DR-TB;



Considering the latest/ updated WHO Guidelines, Treatment Regimens are duly consulted and approved by the Technical Unit with the expected number of patients to be treated in a specific regimen and over an estimated period of treatment duration per the applicable regimen.

Medicines are selected which are either recommended/ approved by the:-

WHO Prequalification of Medicines Program (PQP) or Stringent Drug Regulatory Authority (SRA), or Expert Review Panel (ERP).

The selection of each individual or combination of drugs is made in close consultation and with the approval from the relevant stakeholders, not limited to PSCM Unit/MDR Unit / NTP Management/NTP Finance /GDF/GLC/TGF.

- Selection is further based on disease prevalence, efficacy, safety evidences and Drug Resistance patterns.
- Updates/ international recommendations and national standard treatment guidelines are also kept in mind while selecting the medicines.

A systematic approach is applied in treatment selection taking in consideration the patients previous history of Second Line Drug (SLD) use and the Drug Sensitivity Test (DST) pattern of each case to ensure a minimum of four essential or near essential core drugs for each treatment regimen. Often the patient requires 5 or more drugs to provide adequate treatment.

Currently children are treated with adult formulations that have to be, cut crushed and mixed. This results in incorrect dosing, prolonged hospitalization, and significant staff time for preparing and delivering

medications. However, dispersible formulation of Second-Line Drugs for the Treatment of MDR-TB in Children are available and being used in the treatment of children weighing less than 25 kg and under 14 years of age. These are different formulations of already existing drugs to make treatment of children *easier, safer, and more tolerable*. The major benefits of dispersible DR-TB formulation for children are:-

- Scored to ensure consistency in dosing;
- Dispersible to dissolve in water;
- Smaller sizes for more precise dosing and easier administration;

Quantification

Quantification is a process of estimating quantities and costs of products required for a specific health program during a specific period and determining the timeline/s when orders should be placed and delivered to ensure optimal and uninterrupted supply. Quantification exercise at NTP is conducted bi-annually by the CMU PSM_Working Group, this exercise helps to receive the products with *longer expiries, comparatively strong vigilance and control on over/ under-stocking and any stock outs*. The following parameters are used for quantification of ATT Medicines:-

- Stock on Hand at Central;
- Stock on Order with the International PA;
- Actual enrolment & targets in PF by the program; &
- Stock requirements for the upcoming period.

QuanTB software is an added advantage for the near-to-accurate and quick quantification of ATTs (including SLDs). The forecasted quantities projected in QuanTB are compared with Actual Utilization to weigh and reach to a real-time data.

Procurement

Post completion of afore-defined two critical steps, the quantities ascertained and formally approved by the Program and TGF-CT, procurement is put to process and orders are directly placed to Global Drug Facility (GDF) on a pre-defined “Procurement Request Form" (PRF). Before placing any order lead time for delivery of each drug in NTP’s central warehouse is considered as the foremost factor in mind.

As a pre-requisite for completion of each procurement order, Pro-Forma Invoice(s) / Sales Acknowledgement(s) is received from GDF after the Budget allocation/ disbursement from TGF. These are reviewed at NTP and after the due approval of National Coordinator/ National Program Manager (NPM) are sent back to GDF to proceed for supply. GDF releases Work Order(s) to IDA (*the GDF Procurement agent*).

IDA procures these drugs from WHO Prequalified Pharmaceutical Manufactures from all across the Globe, through a competitive bidding process; and the quality of the drugs are assured through pre and post shipment quality inspection and testing. The usual lead time is 6-8 months from the date of disbursement of funds to IDA.

Storage

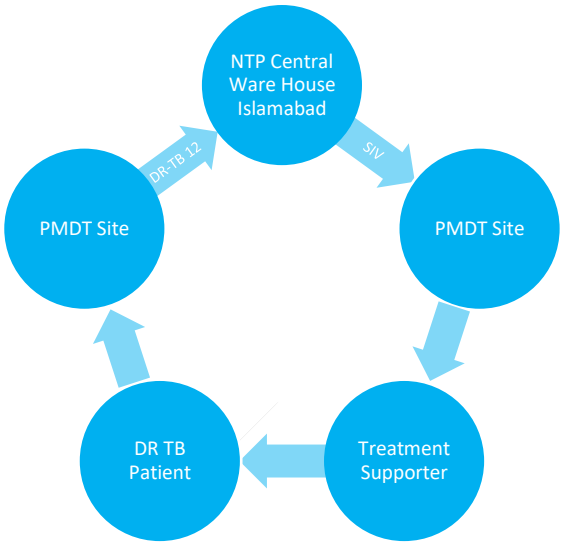
A strong warehousing network plays a vital role in the overall supply chain management of drugs and related programmatic needs in terms of different commodities and ultimately leads to success of every project/ program. Main functions (not limited to) of storage of program commodities, per globally best practicing storage practices are:-

- To preserve the quality of medicines received in-country, all these are and must be stored in a *dry, well-ventilated, well lighted, secure and conducive* premises that offer protection from direct sunlight and dust;
- Temperatures should normally be maintained between 15°C and 25°C;
- Transport arrangements should be secured to ensure that quality of products is guaranteed all along the distribution channel; and right up to the end-beneficiary i.e. TB patient.

Distribution from the Central Level

Distribution of SLDs and all other program commodities, from Central Warehouse to PMDT Sites is practiced on following key standards (not limited to):-

- It takes place on quarterly basis and/ or as and when needed;
- Pull System of Distribution i.e. Medicines are issued on the official demand of site(s), is being followed since Q-1 2017;
- Demand from PMDT sites, duly received on "DR_TB_012_SLD_Demand" is put to process for internal approvals and ultimate distribution to requesting site;
    - Above said demand form mandatorily consists of the monthly consumption of SLDs in the previous quarter;
    - The balance at-hand on the last day of reporting quarter;
    - 33% buffer is provisioned on the quantities, for catering the need for new enrolments.



SLD Management at the PMDT Site:

Following Standard Operating Procedures (SOPs), defined by NTP, are to be followed all across the PMDT sites:-

SOPs for drug forecasting and initiation of demand to NTP:

1. Demand will be initiated by the Pharmacist(s) based at PMDT Site/s, with due considerations of average utilization of SLDs and stock on-hand on DR-TB 12;
2. MDR Physician will thoroughly review the demand and approve the quantities demanded;
3. The scanned and excel sheet of the approved demand of the site will be submitted by the PMDT Site Pharmacist, through an email to the Manager Supply Chain NTP and copying to all concerning staff at PTP & NTP;
4. Manager Supply Chain NTP, will review the demand in consultation with DR-TB Unit and keeping in mind the availability/ stock situation. After the approval of National Program Manager / Deputy National Coordinator NTP will finally forward the demand to the warehouse Manager for transportation.
5. Warehouse manager will inform on the same email about the delivery schedule and quantities being transported.
6. Pharmacist of PMDT Site will acknowledge the receipt of the stock on the same email along with his comments regarding the quality & quantity of the transported stock.

SOPs for Goods Receiving at PMDT Site, dispatched from NTP

1. Site Pharmacist will receive the goods shipped from NTP via TCS.
2. Will check the number of cartons physically before stamping and signing the TCS receipt / NTP Store Issuance Voucher (SIV)
3. Site pharmacist will check all the medicines its batches, expiries and quantities (Quantities, Batches and Expiries should be as per SIV)
4. After inspection pharmacist will receive the goods, sign and stamped the original SIV along with his comments regarding the quality & quantity of the transported stock.
5. Pharmacist will then Store the goods in specified location at specified temperature (15-25^0 C).

SOPs for medicines dispensing to DR TB patient(s) from PMDT Site

1. Pharmacist need a prescription of each patient with patient's weight, dose, frequency, & assigned ENRS number.
2. Pharmacist will recheck each patients Rx for dose and frequency, & will also talk to the concerned Doctor if any intervention is needed.
3. Once the Rx is final, Pharmacist will enter its data in Patients consumption matrix, & will arrange to dispense its SLDs accordingly.
4. Pharmacist will dispense and label individual prescriptions for 30 days and pack the stock in zipper bag, mark with Name/MR Number.
5. Pharmacist will also update its entry in stock register and bin card.
6. Rx will be file for Pharmacy record & future Dispensing.
7. In case of any changed & Stopped Rx, or if Patient get cured, died, default, transferred out or transferred in, Pharmacy will need its information in writing to update all sheets & for future dispensing & record keeping.
8. Before closing the Pharmacy, the following exercise must be done routinely,
    * Bin cards should be maintained on daily basis.
    * check and tally the physical stock with bin card and stock register.
    * Maintain record for patient's prescription.
    * Maintain record of all changed prescription.

Section 12:

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 where data are analysed and used for management. The data thus collected is disseminated by NTP data to national and international stakeholders.

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 has in addition to the responsibilities explained above at provincial level, also responsibilities 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.

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 entered in a Presumptive TB register and referred to laboratory with a Request form for sputum smear microscopy and Xpert testing **(TB 05)**. Complete personal information and results are recorded in **TB04 Laboratory register.** Results are provided back to medical Officer of BMU who decides about the diagnosis of patient. The diagnosed RR-TB case is referred to PMDT after making relevant entries in OPD and TB register. See also Annex 6 Recording and reporting of laboratory results from facilities with or without Xpert.

In PMDT patient is received by DOTS facilitator Case Management who prepare patient file. Following data recording tools are used at PMDT site.

Table 34 Recording tools used in PMDTs

Form No.	Form Name	Description
DR-TB 00	History and Physical Examination Form	This form is checklist for history taking and physical examination of newly diagnosed DR-TB patient and should be filled by the MDR clinician as a first step in the enrolment process during the initial meeting with the patient. Information entered into this form is used as a baseline for the completion of DR-TB 01 Patients Treatment Card.
DR-TB 01	Patients Treatment Card	When a decision is made to enroll a patient on DR-TB treatment the DOTS facilitator Case Management at the PMDT site fills the Treatment Card when the patient is actually starting treatment. This card is the most important instrument for following the patient and needs to be updated regularly since it represents the primary source of information to complete. A copy of the card may be used as a notification form and later also to report the final outcome of treatment. The guidelines recommend that patients infected with strains with relatively simple resistance patterns (H, HS, HE and HZ) stay in the District BMU Tuberculosis Register, where a modified short

		chemotherapy course can be provided (for more information please refer to the treatment strategy chapter of this guidelines or National Guidelines for Tuberculosis control in Pakistan). Patients infected with more complicated mono- and poly-resistance strains (involving Rifampicin Resistance) should be treated at PMDT site and recorded in PMDT R&R tools.
DR-TB 02	Patient's Identity Card	This card is filled in by DOTS facilitator Case Management and handed over to the patient on the first day of enrolment and before leaving the PMDT treatment site. This card contains information related to treatment, daily intake of medicines (DOT) and next scheduled follow-ups. The card, or a copy of the card, must always follow the patient (e.g. from PMDT Site to an ambulatory facility).
DR-TB 03	Electronic Nominal Registration System (ENRS) of DR-TB	The DR- TB treatment register is intended primarily to keep a record of those data that are important for generating indicators and reports of patients on second-line regimens. In contrast to the BMU register, it is restricted to patients who have actually started on a second-line TB treatment regimen. This register is also commonly used to follow, at a glance, the adequacy of testing and treatment decisions. The ENRS is updated regularly from individual DR-TB 01 Treatment Card and patient's file by MDR physician weekly and before reporting to PTP and NTP. Patients should be recorded consecutively by their date of registration. ENRS is excel based and will be online soon. Only PMDT site, PTP and NTP has access to the data.
DR-TB 03	DR-TB Patient's Register	This is the paper based/hard copy of ENRS register with limited data for archiving. This register is used for data validation during quarterly intra district surveillance meetings and monitoring visits.
DR-TB 04	DR-TB Laboratory Register for PMDT Site	This register is used by PMDT site to record diagnostic and follow up laboratory testing information of DR-TB patients undertaking more advanced specimen testing (culture, Xpert MTB/RIF, LPA, DST). The method of diagnostic testing (culture or Xpert MTB/RIF) is indicated under "Type of examination". Results of tests undertaken for monitoring of patients on treatment are likewise entered in separate rows.

Monitoring Treatment Outcome of Patients enrolled on Second Line Treatment
For RR case category and treatment outcome definitions please refer to Section 1.

Data Reporting Tools

These reports are generated electronically from ENRS by PMDT sites and are reported on quarterly basis. Following reports are to be reported to provincial and national programme.

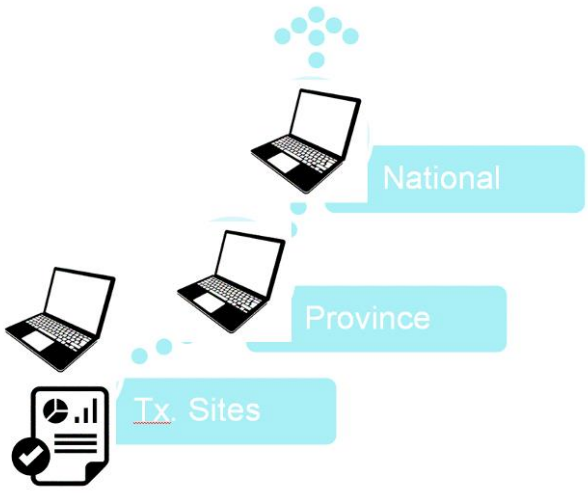
Table 35 Reports to provincial and national TB programme

Form No.	Form Name	Description
DR-TB 07	Quarterly Report on RR-TB Enrollment on Second Line Drugs	The program is responsible to ensure that all patients in whom RR-TB is diagnosed are placed on appropriate treatment in the shortest time possible. Early detection is intended to ensure they get an appropriate drug regimen from the start and lower risks of further amplification of drug resistance. Four minimum indicators have been identified to assess the number and proportion of RR-TB patients who have been started on treatment. The pattern of recruitment by age-group and gender should be monitored. The HIV status of confirmed RR-TB cases assesses both the coverage of HIV testing. The period of assessment is 3 months. These are counted from January to March, April to June, July to September and October to end December. Indicators are measured in the month after the end of the 3-month period. All data can be extracted from the ENRS treatment register.
DR-TB 08	Quarterly Report on 6th month Assessment of patient enrolled on Second Line Treatment	Treatment for RR-TB typically takes from 11-20 months or more. The program often needs an indication of how patients are faring well before final outcomes can be assessed, typically two years after the start of enrolment. This is particularly important when a new PMDT and/or treatment regimen starts. Assessing smear and culture conversion (for confirmed pulmonary cases) and death by six months is widely used as a proxy of final outcomes. Information on LTFU by 6 months is helpful. It is also useful to know how many patients started on second-line drugs for RR turned out not to be Fluoroquinolone (FQ) resistant or XDR at start. This evaluates the effectiveness of the treatment algorithm in reserving treatment for patients who really need it and avoiding a potentially toxic regimen in patients who do not. The period of assessment is 3 calendar months (quarter). All patients registered and starting treatment during the period of assessment are included in the calculation. Indicators are measured one year after the end of the quarter of assessment. This gives sufficient time for culture results at month 6 to be issued and retrieved. All data can be extracted from the ENRS.
DR-TB 09	Quarterly Report on Second Line Treatment Outcome	For the program, the final outcome is the most important direct measurement of the effectiveness of control program in terms of patient care. All confirmed RR-TB patients entered on the treatment register should be assigned one of six mutually exclusive outcomes at the end of their therapy. The outcome categories are aligned to the ones in use for treatment of drug-susceptible TB, and the definitions are the same with the exception of cured and failed. Cases who are not evaluated due to transfer, loss to follow up or “still on treatment” at the moment of final assessment are grouped together. All patients should be assigned the first outcome they experience for the treatment being evaluated. Success (cure and completion) and death should be measured separately for HIV positive individuals in high prevalence situations. The period of assessment is 3 calendar months (quarter). All patients registered and starting treatment during the period of assessment are included in the calculation. Indicators are

		measured 2 years after the end of the quarter of assessment. With the introduction of shorter MDR-TB regimen (11 months), the outcome of STR cohort may be reported after 15 months (5 quarters after enrolment). This gives sufficient time for most patients to complete their treatment and for the final culture results to be issued and retrieved. All data can be extracted from the ENRS.

Data Flow

The data entered from patients' files into ENRS by the PMDT sites are used to generate reports which are sent electronically to provincial and national program. The data which is reported routinely are ENRS, SLD stock status reports (DR-TB 12) and quarterly reports on enrollment, interim assessment and treatment outcome. Following is the flow of data from PMDT to NTP.



PMDT

- Record at PMDT Sites are managed in patients files and case wise data is entered into excel sheets.
- These sheets are reported to provinces and NTP

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. The quarterly reports are validated by tallying it with DR-TB 03 paper-based RR register or ENRS. The register or ENRS are randomly cross checked with patient's file and DR-TB01. The validation process is usually carried out during Intra-district quarterly meeting or during monitoring visits. Paper based registers are requirement of hospitals and M&E system so that data cannot be manipulated and can be archived.

National and provincial program staff conduct regular supervisory visits to the PMDT using the information system as well as meetings with staff from different levels. The MDR physician at the PMDT site is responsible to regularly (at least weekly) compare the DR-TB 03 ENRS Patients Register with the DR-TB 01 Patients treatment card to ensure that all data is updated regularly and in a timely manner rather than waiting until the end of the month to complete all the monthly update.

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), lab technician of BMU and PMDT staff in the district come to district headquarter level for one day meeting. PMDT staff bring the recording instruments i.e. DR-TB01, DR-TB03 and three reports i.e. DR-TB07, DR-TB 08 & DR-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.
- **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 all PMDT sites in the province and individual data of each site. Updates and trend analysis is shared. This meeting is primarily aimed to review the performance of PMDT 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. PMDT sites are being provided with access to DHIS2 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 later case-based data entry (tracker system) will be adopted.

Serious Adverse Event Reporting Form"

All serious adverse events should be reported by PMDT staff using the "Serious Adverse Event Reporting form" within 24 hours emailing it to the provincial MDR Unit and NAAC (National aDSM Advisory Committee). (Handbook p 11)

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 program performance.

TB data analysis and use must be done at PMDT, 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.

List of Indicators

Following is the list of key program indicators for programmatic management of drug resistant tuberculosis.

Table 36 Key program indicators for PMDT

Indicator	Calculation	Data Source	Level	Frequency
TB patients with results for Rifampicin Resistance (separately for new and	*Numerator:* Number of pulmonary TB patients registered during a specific time period with results for rifampicin *Denominator:* Number of pulmonary TB patients	Quarterly reports on TB case registration (TB07), TB register	National, Provincial, District, Facility	Annually, Quarterly

previously treated)	registered during a specific time period	(TB03)		
% of pulmonary TB patients with valid test result for Rifampicin Resistance TB (RR-TB) who have RR (separately for new and previously treated cases)	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) registered during a specific time period *Denominator:* Number of pulmonary TB patients registered during a specific time period with results for rifampicin	Quarterly reports on TB case registration (TB07), TB register (TB03)	National, Provincial, District, Facility	Annually, Quarterly
% of RR-TB patients enrolled on RR-TB treatment	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) registered during a specific time period	Quarterly reports on DR-TB case registration (DR-TB07), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
% of RR-TB patients enrolled on RR treatment with negative culture by six months (separate for STR and LTR, and separate for FQ-sens, FQ res and FQ resistence unknown – for all the outcomes)	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment with negative culture by month six of treatment *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Interim results (DR-TB08), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
Rifampicin resistant TB patients on second-line treatment who died by six months	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment who died by month six of treatment *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Interim results (DR-TB08), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
Rifampicin resistant TB patients on second-line treatment who were lost to follow-up by six months	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment who were lost to follow-up by month six of treatment *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment	Quarterly reports on DR-TB Interim results (DR-TB08), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly

	during a specific time period			
Rifampicin resistant TB patients cured (separate for STR and LTR, and separate for FQ-sens, FQ res and FQ resistence unknown – for all the outcomes: completed, failed, died, LTFU, not evaluated, still on treatment)	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during the period of assessment and are declared cured *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Treatment Outcome (DR-TB09), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
Rifampicin resistant TB patients completing treatment	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during the period of assessment and have completed treatment *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Treatment Outcome (DR-TB09), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
Rifampicin resistant TB patients whose treatment failed	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during the period of assessment and have failed treatment *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Treatment Outcome (DR-TB09), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
Rifampicin resistant TB patients who died	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during the period of assessment and have died. *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Treatment Outcome (DR-TB09), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly
Rifampicin resistant TB patients lost to follow-up	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during the period of assessment and	Quarterly reports on DR-TB Treatment Outcome (DR-	National, Provincial, Facility	Annually, Quarterly

	lost to follow-up *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	TB09), DR-TB register (DR-TB03)		
Rifampicin resistant TB patients not evaluated for outcome	*Numerator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during the period of assessment and not evaluated *Denominator:* Number of pulmonary TB patients with rifampicin resistance TB (RR-TB) enrolled on second-line treatment during a specific time period	Quarterly reports on DR-TB Treatment Outcome (DR-TB09), DR-TB register (DR-TB03)	National, Provincial, Facility	Annually, Quarterly

Section 13:

Preparedness of TB Control Program in Emergencies

Any sort of emergencies may result in breakdown of health services delivery functions. The consequences may result in decreased case notification, increase in lost to follow up and risk of emergence of drug resistance. Continuation of health delivery services during emergencies is important yet challenging task for TB control program.

With the outbreak of COVID-19 pandemic in Pakistan with lockdown of the population and pressure on the health services, NTP Pakistan appropriately responded to the situation with special focus on the following aspects of TB case management across the country.

Rapid assessment was conducted for situational analysis on the following:

- Assess change in TB case notification (DS & DR TB) during COVID-19, by ensuring that the R&R system was functioning, and documenting a dramatic decline.
- Assess preparedness of primary health care facilities to manage COVID suspect in terms of availability of optimum infection control measures.

Furthermore, the program provided stewardship and leading role by developing relevant advisories and guidance document to ensure:

- For TB patients to continue treatment:
    - Uninterrupted provision of treatment services at healthcare facilities, ensuring ATT drug delivery to both DS and DR TB patients on treatment, including home delivery to patients homes for 1-3 months at a time
    - Provision of social support to DRTB patient for treatment adherence
    - Uninterrupted drug supply and to seek health care at nearest hospital in case of experiencing of drug related adverse event.
- To ensure that TB patients were diagnosed timely:
    - Provision of step wise guidance to health facilities with development of an diagnostic algorithm for patient with respiratory symptoms in OPDs to detect both TB and Covid-19, especially at resource limited settings,
- To reduce impact of Covid-10 pandemic by:
    - Optimum implementation of infection control measures at health care facilities, labs and households to prevent disease transmission both of health staff and patients.
    - Information campaigns to prevent stigma of both TB and Covid-19.

Ministry of National Health Services, Regulations and Coordination and National TB Control program needs to provide leadership and stewardship in emergency situation. Establishment of coordination among stakeholders is also important may contribute in successful roll out of interventions during emergency. Synergies are possible, such as using Xpert modules also to diagnose Covid-19. NTP will also develop contingency guidelines for enhanced preparedness and handling during crisis.

NTP need to be always alert to address such unforeseen emergencies and respond appropriately in the best interest of patients.

References:

- NTCP. Covid-19 and TB care in OPD settings. Operational guide. April 28, 2020.
- WHO Information Note Tuberculosis and COVID-19 Date: 12 May 2020. COVID-19: Considerations for tuberculosis (TB) care (https://www.who.int/docs/default-source/documents/tuberculosis/infonote-tb-covid-19.pdf?sfvrsn=b5985459_18)

Section 14:

Operational Research

National TB Control program is committed to develop interventions to achieve END TB goals and targets in the context of Pakistan. The implementation research is meant to inform how effective, acceptable, feasible and efficient these interventions are. The Program has been encouraging its staff and partners to add implementation research component to the innovation and intervention scaling activities. NTP has during several years trained a large number of health staff in operational research, publishing numerous papers. OR is a component of the GF project. In this regard, the National and Provincial TB Control Programs and partners will continue using the routinely collected data, supplemented by data collection and surveys as and when needed, to uncover the ways of delivering more effective, efficient and equitable TB, MDR-TB and its associated care.

The program implementation research process can broadly be outlined as follows:

1. Identify and understand the program implementation challenges, through interacting with stakeholders at multiple levels, finding the most urgent research questions.
2. Prioritize the listed implementation challenges/ problems through an open and transparent stakeholder consultation (short and medium-term program research activity), developing research agendas.
3. Develop contextualized strategies/interventions, through program facilitated technical working group process, to address the implementation challenges.
4. Develop adequate and feasible multi-method research design to evaluate the early implementation of the agreed intervention/ strategy to address the challenge/ problem, developing research protocols, and submit them for ethics approval.
5. Early implementation of intervention and collect data on care delivery (mainly quantitative) and related experiences (generally qualitative)
6. Compile, analyze and interpret research data, by engaging both implementers and researchers; preferably through triangulating multiple data sources/ types and writing up the research findings in published papers,
7. Respond to the research findings i.e. plan scaling of intervention (with or without further adaptation), wider dissemination of the experience (through publication and presentations), and plan further research as deem needed.

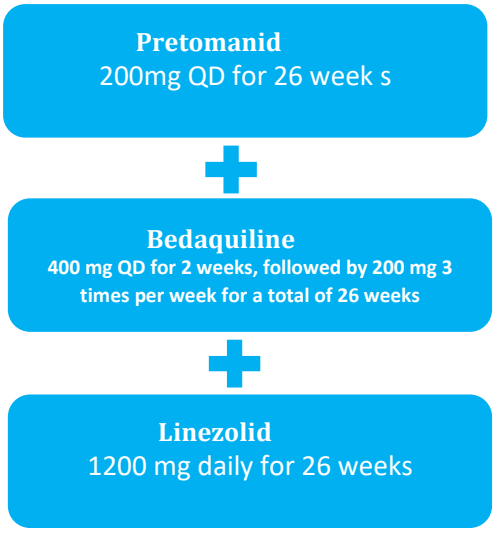
The core principles for the program implementation research will remain:

a. The implementation research generates valid knowledge to inform an important program consideration.
b. The research methods and conduct meet the technical and ethical standards/ requirements.
c. The research applies systems orientation; also ensure multi-disciplinary inputs, as deem needed.

Currently (Sept 2020) two OR projects regarding RR-TB have been promoted by WHO and is in the pipeline with NTP: BPal and modified STR.

BPal Regimen for treatment of RR-TB with FQ-resistance

An all oral short, fixed dose 3 drug (Pretomanid, Bedaquiline, Linezolid) combination was used for 6-9 months in patients with highly resistant TB in a trial (Nix-TB study) in South Africa which showed improved outcomes (90% cure rate) with marked reduction of symptoms and improvement in overall health status of patients. The rationale behind use of BPal regimen involves use of three drugs having potent bactericidal activity and different mode of actions for a shortened time period.



As per latest WHO recommendations, BPal (bedaquiline, the new drug pretomanid and linezolid) regimen may be used under operational research conditions in patients with multi-drug resistant TB with fluoroquinolone resistance and who have either had no previous exposure to Bedaquiline and linezolid or have been exposed for no more than 2 weeks.

The patient needs careful selection to enable effective treatment adherence. Vigilant monitoring of adverse effects is also necessary and needs careful consideration during operational use of this regimen. It is not advised to include pregnant, lactating women and children for this intervention as these subgroups were not tested during the trial. The treatment must be administered closely to monitor the acquisition of drug resistance. Measures to support patients through home visits by staff and financial support is also paramount for improved patient adherence.

The intervention must be implemented under strict aDSM protocols for timely management of adverse effects and reporting of any adverse drug reactions to relevant drug authorities through a formal process.

In case of adverse effects (myelosuppression, peripheral neuropathy and optic neuropathy), linezolid dosage (1200 mg per day) maybe reduced to 600 mg or 300 mg daily or temporary cessation of linezolid is also permitted for up to 35 consecutive days. If toxicity prohibited further treatment with linezolid, patients could remain on Bedaquiline and pretomanid, provided that they had received the 1200 mg per day dose for at least the first 4 consecutive weeks, were sputum smear negative, and were responding to treatment based on clinical monitoring and follow-up.

Patients who receive BPaL need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing. According to the product label of pretomanid, baseline assessments before initiation of the BPaL regimen include assessments for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) and the conduct of laboratory tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin, complete blood count and serum potassium, calcium and magnesium (which should be corrected if abnormal). Treating clinicians should also obtain an ECG before initiation of treatment.

Monitoring after the completion of treatment was carried out monthly for months 1–3, and 3-monthly thereafter. Follow-up after treatment completion was for a total of 24 months.

Details on a generic operational research protocol, data collection and other aspects that can be adapted for the BPaL operational research can be found in the ShORRT research package developed by WHO and TDR *(36)*. ShORRT (Short, all-Oral Regimens For Rifampicin-resistant Tuberculosis) Research Package. Geneva:

World Health Organization and the Special Programfor Research and Training in Tropical Diseases; 2015 (https://www.who.int/tdr/research/tb_hiv/shorrt/en/, accessed 1 June 2020).

Currently (Sept 2020) the BPal protocol has not yet been approved in Pakistan. The main challenge in its use in Pakistan may be the delay in LPA results in many areas (to identify FQ resistance) so that Bdq has not been used more than two weeks. The high rate of severe adverse events also requires strict aDSM. But a 6 months regimen could be a large improvement for RR-TB patients who today have low success rates with LTR-2.

Modified Shorter Treatment Regimen

As per WHO recommendations, new combinations in all-oral short treatment regimens can be tried under operational research conditions. Since Jan 2020 injectable containing STR has been replaced with all oral STR with Bedaquiline replacing amikacin. The rationale behind this change was mainly injectable related irreversible hearing loss and its effects on life of the patient as a whole. The current revised STR regimen which is programmatically in implementation is as follows:

6Bdq, Mfx/Lfx, Eto, Cfz, Z, H high dose, E/5 Mfx/Lfx, Cfz, Z, E

However, this regimen still contains drugs and combinations which could lead to unfavorable outcomes. In this context, ASD with NTP and PTP has developed a protocol on modified short treatment regimen. The rationale behind providing the programs with freedom to apply certain STR treatment modifications is to generate data to determine effectiveness, safety, feasibility and impact on quality of life of patients with DRTB.

As already implemented in South Africa under programmatic conditions, a modified STR is available where changes in relation to replacement of potent and less harmful drugs for safer time period is used. The regimen starts with seven drugs Linezolid (LZD), Isoniazid high dose (INH high dose), Bedaquiline (BDQ), Levofloxacin (LFX), Clofazimine (CFZ), Pyrazinamide (Z) and Ethambutol (E). The total duration of the treatment is 9-11 months with 4 intensive months extendable to 6 months depending upon the response of the treatment (smear conversion and clinical response) followed by 5 months of continuation phase. The modified STR regimen is as follows:

2 Lzd-Bdq-Lfx-Cfz-Z-E-H (high dose) / 4 Bdq-Lfx-Cfz-Z-E-H(high dose) / 3 Lfx-Cfz-Z-E

Changes made in the current modified STR regimen are as follows:

- Linezolid: Added in the regimen to protect Bdq in early stages where FQ resistance is yet to be established (invalid LPA results). It is to be given for first two months to strengthen the intensive phase in conjunction with other potent drugs. Mostly Lzd related neuropathy occurs in patients with more than 2 months use however, myelosuppression is dose dependent and can occur anytime and needs strict CBC monitoring throughout treatment cycle.
- INH high dose: included for intensive phase of 4 months if INH sensitive or with mutation (inhA) showing low level resistance). It can be extended in conjunction with extension of intensive phase to month 6 due to persistence or recurrence of smear positivity by month 4.
- Bedaquiline: is given for 6 months regardless of duration of intensive phase and maybe withdrawn in case of toxicity or other contraindication.
- Levofloxacin: replaces moxifloxacin to reduce risk of QT prolongation with Bdq and Cfz. It is given for full duration of treatment.
- Clofazimine, Pyrazinamide & Ethambutol: to be given for full treatment duration.
- Ethionamide: will not be used in this research due to occurrence of safety and efficacy concern side effects (GI) and high prevalence of cross resistance with inhA mutation.

Eligibility Criteria

Inclusion Criteria:

- ≥15 years of age; is willing and able to give informed consent to be enrolled in the research project and for follow-up (signed or witnessed consent if the patient is illiterate).
- Has bacteriologically or molecularly confirmed TB with evidence of resistance to at least rifampicin.

- Has no resistance to Fluoroquinolones; no known previous exposure (of > 1 month) or intolerance to 1 or more second-line drugs in the shorter MDR-TB regimen

Exclusion Criteria:

- DST showing infection with a strain resistant to Fluoroquinolones (or DST results not available).
- previous exposure to or intolerance to second-line anti-TB drugs in the intended shorter MDR-TB regimen for more than one month
- pulmonary TB that is clinically severe, or advanced (i.e. parenchymal lesions) or disseminated;
- unable to take oral medication; or to attend or comply with treatment or follow-up schedule
- or taking medication contraindicated with the medicines in the RR/MDR-TB regimen
- known insufficient functioning of: heart (QTcF>500ms), or liver (ALT/AST>5 UNL), or kidneys (creatinine>2 UNL or creatinine clearance <50ml/min)

In addition to Bpal and modified short treatment regimen, there might be other regimens which can also be trialed under OR conditions.

Section 15: Annexes

Annex-1:

List of major references, in addition to footnotes, more general documents consulted.

The revision was based on a number of documents including those listed below. Key references include JPRM 2019/GLC 2019 (GLC report includes the main issues from the JPRM), followed up in NSP and GF application 2020 expressing the current thinking in the NTP and partners.

WHO Consolidated and Operational Guidelines 2020 describes new recommendations and the draft rGLC recommendations June 2020 describes interpretations in EMRO region. The Union Field Guide 2018 focuses on programmatic issues with standardized regimens, and published papers by Union raised concerns about the WHO recommendations which were discussed.

The revised handbook/guidelines were coordinated with the 2019 NTP Guidelines and was based on routine data as presented in the NTP 2019 Annual Report and more updated information provided for the revision.

- National Strategic Plan (NSP) 2020-2023,
- GF application (Concept Note),
- NTP Annual Report -2019
- NTP TB Laboratory Network and National TB Reference laboratory.
- NTP National Guidelines-2019
- Pakistan TB Profile 2019 (Draft)
- WHO Consolidated Guidelines on Treatment of DR-TB (June-2020)
- WHO Operational Guidelines on DR-TB (June-2020)
- WHO advise on Lab/Diagnostics (June 2020)
- JPRM (Joint Programme Review Mission)-2019
- GLC Report 2019 (part of and includes DR-TB issues from JPRM in more detail)
- rGLC recommendations from meeting June-2020 (informal, still draft),
- National PMDT Guidelines Revised Nov-2014
- Union Field Guide for the management of Drug-resistant Tuberculosis -2018
- Ethical Review application for the project "All-oral shorter treatment regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB): Evaluating their effectiveness, safety, feasibility, cost-effectiveness and impact on the quality of life of patients in Pakistan.
- **Relevant Scientific Papers,**
    - *Van Deun A, et al. The perceived impact of isoniazid resistance on outcome of first-line rifampicin-throughout regimens is largely due to missed rifampicin resistance. PLoS One. 2020;15(5): e0233500. Published 2020 May 18.)*
    - *Chiang CY, Trébucq A, Piubello A, Rieder HL, Schwoebel V, Van Deun A. The looming threat of bedaquiline resistance in tuberculosis. Eur Respir J. 2020;55(6):2000718. Published 2020 Jun 4.)*
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Annex-2:

Coverage of universal rifampicin testing and trend of Rifampicin Resistance

(Ref. TB laboratory Network and National Reference Laboratory, Annual Report 2019)

Universal rifampicin testing and trend of rifampicin resistance.

For monitoring of this indicator the data need to be collected from TB Register. However, problems are still encountered with regard to completeness of recording and reporting.

Table-37: Coverage of universal rifampicin testing and trend of Rifampicin resistance

		ALL B+ ve TB	B+ ve NEW	B+ ve PT	Unknown
2017	**B+ cases notified**	**144161**	**128805**	**15241**	**115**
	Number with Rif results	54991	37059	11380	6552
	% B+ with RMP results	38.1%	28.8%	74.7%	NA
	Number RMP-Resistant	3475	1831	1202	442
	RMP-Resistant%	**6.3%**	**4.9%**	**10.6%**	**6.7%**
2018	**B+ cases notified**	**144121**	**128001**	**15925**	**195**
	Number with Rif results	72634	55019	14815	2800
	% B+ with RMP results	**50.4%**	**43.0%**	**93.0%**	
	Number RMP-Resistant	3842	2476	1252	114
	RMP-Resistant%	**5.3%**	**4.5%**	**8.5%**	**4.1%**
2019	**B+ cases notified**	**135909**	**122337**	**13423**	**149**
	Number with Rif results	83823	71841	11982	0
	% B+ with RMP results	**61.7%**	**58.7%**	**89.3%**	**0.0%**
	Number RMP-Resistant	3820	2946	874	0
	RMP-Resistant%	**4.6%**	**4.1%**	**7.3%**	

Drug Susceptibility Testing (DST): In 2019, altogether 6966 DST for *Mycobacterium Tuberculosis* were performed in the country including 85% by Public and Private (IHK) sector laboratories supported by the Global Fund grant.

Among all DST performed from pulmonary isolates (6057), 42.6% were rifampicin resistant whereas among EPTB isolates tested (909), 5.4% were rifampicin resistant. (Table-19)

Annex 3: Fluoroquinolone Resistance in RR/MDR-TB 2019

From TB laboratory Network and National Reference Laboratory, Annual report 2019, table 21
Fluoroquinolone is one of the core drug in management of DRTB. Pakistan has high level of FQ resistance compared to global trend. A gradual decline is seen in FQ resistance compared to previous five years, across all provinces. Table-20 is showing trend of FQ resistance in provinces. In 2019 compare to other provinces, lowest FQ resistance was reported in KP. However, constant trend of lower FQ resistance is noted in Sindh in previous years.

Table-38: National Trend of FQ Resistance in RR/MDR TB cases.

Region	Lab		2013	2014	2015	2016	2017	2018	2019
			PTB	PTB	PTB	PTB	PTB+EPTB	PTB+EPTB	PTB+EPTB
National		DST(N)	2213	2359	2292	2363	2862	2892	2389
		FQr(n)	1121	1114	996	1126	1104	1141	894
		FQr(%)	**50.7%**	**47.2%**	**43.5%**	**47.7%**	**38.6%**	**39.5%**	**37.4%**
Punjab +ICT+ Allied	NRL	DST(N)	269	623	894	1065	1255	1453	1293
		FQr(n)	127	315	475	564	604	668	560
		FQr(%)	**47.2%**	**50.6%**	**53.1%**	**53.0%**	**48.1%**	**46.0%**	**43.3%**
Khyber Pakhtunkhwa	PRL KP	DST(N)		70	189	158	312	318	230
		FQr(n)		31	77	59	154	119	56
		FQr(%)		**44.3%**	**40.7%**	**37.3%**	**49.4%**	**37.4%**	**24.3%**
Sindh	PRL Sindh & TIH	DST(N)	380	755	971	1033	1178	981	733
		FQr(n)	135	272	327	443	375	292	223
		FQr(%)	**35.5%**	**36.0%**	**33.7%**	**42.9%**	**31.8%**	**29.8%**	**30.4%**
Balochistan		DST(N)						40	51
		FQr(n)						10	16
		FQr(%)						**25.0%**	**31.4%**
ALL	AKU	DST(N)	1564	911	238	110	117	100	82
		FQr(n)	859	496	117	61	71	52	39
		FQr(%)	**54.9%**	**54.4%**	**49.2%**	**55.5%**	**60.7%**	**52.0%**	**47.6%**

Annex 4: Resistance Conferring Mutation and Interpretations.

1. RIFAMPICIN: - Below is the list of Resistance conferring mutation detected or inferred

Mutation	Result Interpretation	Clinical Implications	Additional Diagnostic Action
rpoB			
D516V	**Resistance to Rif detected**	Rifampicin is not effective.	
H526Y		Rifampicin is not effective.	
H526D		Rifampicin is not effective.	
S531L (S450L)		Rifampicin is not effective.	
Mutation(s) at codons 505-509	**Resistance to Rif inferred**	Rifampicin is not effective	
Mutation(s) at codons 510-513		Rifampicin is not effective	
Mutation(s) at codons 510-517		Rifampicin is not effective	
Mutation(s) at codons 513-519		Rifampicin is not effective	
Mutation(s) at codons 516-522		Rifampicin is not effective	
Mutation(s) at codons 518-525		Rifampicin is not effective	
Mutation(s) at codons 526-529		Rifampicin is not effective	
Mutation/s at codon 530-533		Rifampicin is not effective	

2. **ISONIAZID:** - Below is the list of resistance conferring mutation detected or inferred

Mutation		Result Interpretation	Clinical Implications	Additional Diagnostic Action
katG	**S315T1 /S315T2**	**High level** resistance to H detected.	Isoniazid is likely not effective even at high dose.	No additional diagnostic action required
	Mutation(s) at codon 315	**High level** resistance to Isoniazid (H) inferred.	Isoniazid is likely not effective even at high dose.	
inhA	***c-15t***	At least **low-level** resistance to H detected. Resistance to Eto/Pto detected.	Isoniazid at high dose is likely to be effective. Ethionamide/prothionamide are not effective.	**Optional:** Perform phenotypic DST for H at clinical breakpoint to exclude high level resistance.
	a-16g.	At least **low-level resistance to H detected.** **Resistance to Eto/Pto detected.**	Isoniazid at high dose is likely to be effective. Ethionamide/prothionamide are not effective.	**Optional:** Perform phenotypic DST at CB* for H to exclude high level resistance.
	t-8a	At least **low-level resistance to H detected.** **Resistance to Eto/Pto detected.**	Isoniazid at high dose is likely to be effective. Ethionamide/prothionamide are not effective.	**Optional:** Perform phenotypic DST at CB* for H to exclude high level resistance.

	t-8c	At least **low-level resistance to H detected.** **Resistance to Eto/Pto detected.**	Isoniazid at high dose is likely to be effective. The regimen should be re-evaluated if phenotypic DST shows that the strain is resistant to H at CB. Ethionamide/prothionamide are not effective.	**Optional:** Perform phenotypic DST at CB for H to exclude high level resistance.
	Mutation in the -15 region	**At least low-level resistance to H inferred.** **Resistance to Eto/Pto inferred.**	Isoniazid at high dose is likely to be effective. Ethionamide/prothionamide are not effective.	**Recommended**: Repeat SL-LPA and if the result is confirmed perform phenotypic DST for H at CB.
	Mutation in the -8 region	**At least low-level resistance to H inferred.** **Resistance to Eto/Pto inferred.**	Isoniazid at high dose is likely to be effective. Ethionamide/prothionamide are not effective.	Perform phenotypic DST for H, Eto/Pto at CC.

3. **Fluoroquinolone:** - Below is the list of resistance conferring mutation detected or inferred

Mutation		Result interpretation	Clinical implications	Additional Diagnostic Action
gyrA	**D94N or D94Y**	Resistance to Lfx detected. **High-level** resistance to Mfx detected	Levofloxacin is not effective. Moxifloxacin is not effective.	No additional diagnostic action required.
	D94G	Resistance to Lfx detected. **High-level** resistance to Mfx detected	Levofloxacin is not effective. Moxifloxacin is not effective.	No additional diagnostic action required.
	D94H	Resistance to Lfx detected. **High-level** resistance to Mfx detected	Levofloxacin is not effective. Moxifloxacin is not effective.	No additional diagnostic action required.
	D94A	Resistance to Lfx detected. At least **low-level** resistance to Mfx detected	Levofloxacin is not effective. Moxifloxacin could be used at higher dose. The regimen should be re-evaluated based on phenotypic DST results at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance.
	A90V	Resistance to Lfx detected At least **low-level** resistance to Mfx detected	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated based on phenotypic DST results at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance.

	S91P	Resistance to Lfx detected At least **low-level** resistance to Mfx detected	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated based on phenotypic DST at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance to Mfx.
	Mutation(s) at codon 85 - 89	Resistance to levofloxacin (Lfx) inferred At least **low-level** resistance to moxifloxacin (Mfx) inferred (as mutations different from G88C and D89N cannot be excluded).	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated based on phenotypic DST at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance.
gyrA	**Mutation at codon 90-91**	Resistance to levofloxacin (Lfx) inferred At least **low-level** resistance to moxifloxacin (Mfx) inferred	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated based on the phenotypic DST results at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance.
	Mutation/s at codon 92-96	Resistance to Lfx inferred At least **low-level** resistance to Mfx inferred	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated based on the phenotypic DST results at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance.
gyrB	**N538D**	Resistance to Lfx detected. Mutation associated with at least **low-level** increase in MIC for Mfx detected.	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated if phenotypic DST shows that the strain is resistant to Mfx at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance to Mfx.
	E540V	Resistance to Lfx detected. Mutation associated with at least **low-level** increase in MIC for Mfx detected.	Levofloxacin is not effective. Moxifloxacin could be used at higher dose in combination with additional three or four effective drugs. The regimen should be re-evaluated if phenotypic DST shows that the strain is resistant to Mfx at CB.	**Recommended**: Perform phenotypic DST for Mfx at CB to exclude high level resistance to Mfx.

	Mutation/s at Codons 536-541	Resistance to Lfx inferred At least **low-level** resistance to Mfx inferred	Levofloxacin is not effective. Moxifloxacin could be used at higher.	**Recommended**: Perform phenotypic DST at CB for Mfx.

4. **Second Line injectable:** - Below is the list of resistance conferring mutation detected or inferred

Mutation		Result interpretation	Clinical implications	Additional Diagnostic Action
	AMIKACIN			
rrs	**a1401g**	**Resistance to Am detected**	Amikacin is not effective.	No additional diagnostic action required.
	g1484t	**Resistance to Am detected**	Amikacin is not effective.	No additional diagnostic action required.
	Mutation in the 1400 region	**Resistance to Am inferred**	Amikacin is not effective. **Note.** This recommendation does not apply if phenotypic DST shows susceptibility.	
	Mutation in the 1484 region	**Resistance to Am inferred**	Amikacin is not effective.	**Recommended**: Repeat the SL-LPA test and if the result is confirmed, perform phenotypic DST for Am.
	KENAMYCIN			
eis	**c-14t**	**Resistance to Km detected**	Amikacin is effective. Kanamycin is not effective.	No additional diagnostic action required
	Mutation in the -37 region (such as g-37t)	**Resistance to Km inferred**	Amikacin is effective. Kanamycin is not effective.	No additional diagnostic action required
	Mutation in the -10 to -14 region (such as g-10a or c-12t)	**Resistance to Km inferred**	Amikacin is effective. Kanamycin is not effective.	No additional diagnostic action required
	Mutation in the -2 region (such as c-2a)	**Resistance to Km not detected**	Amikacin is effective. Kanamycin is effective.	No additional diagnostic action required. Note. *No evidence that mutations in this region are associated with resistance*[1]

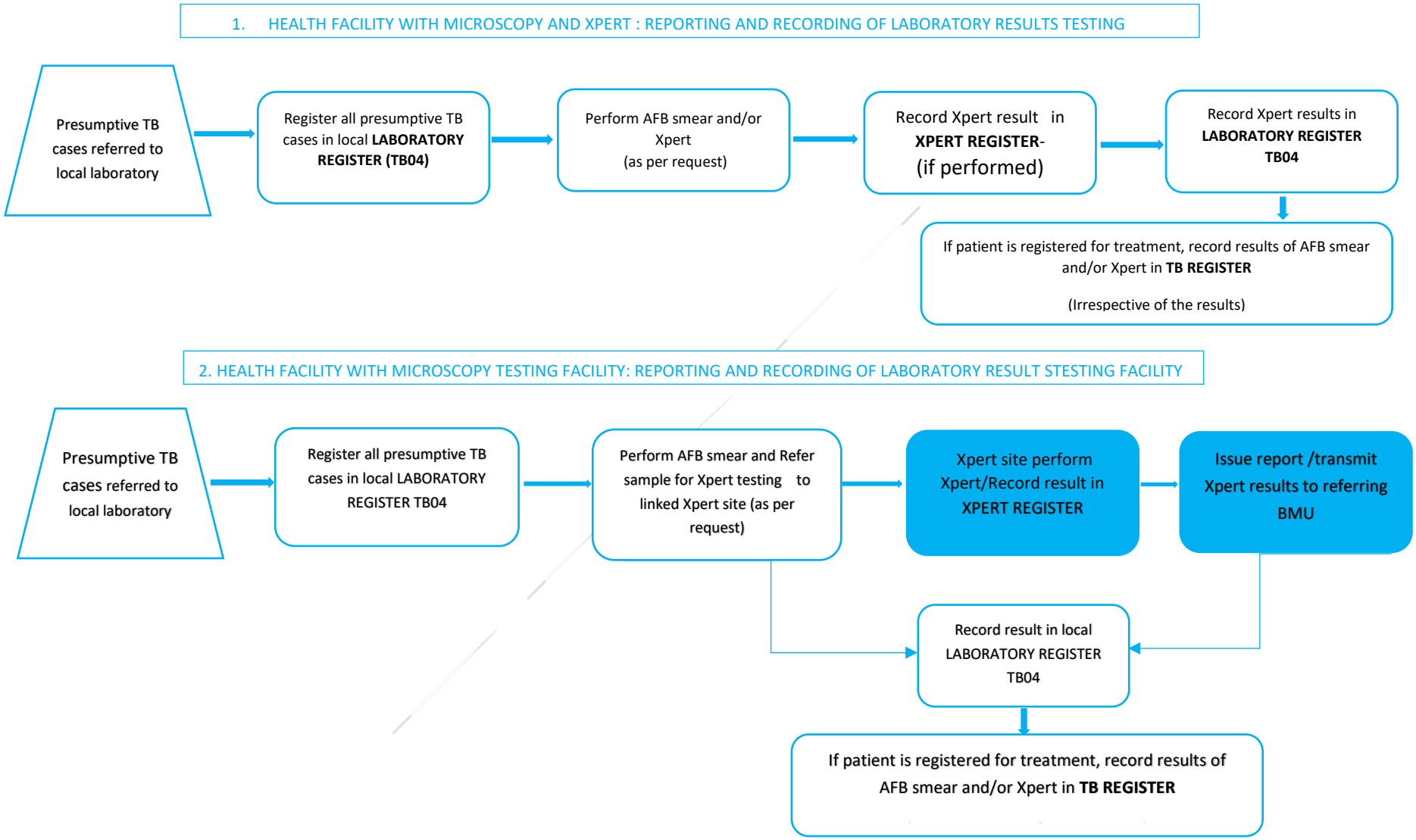
Annex 5:

RR-TB Treatment Outcome Tables 2017-2018 by Regimen and FQ Resistance (From ENRS)

Treatment Outcome of STR (FQ sens or FQ unknown?)										
Year	**Quarter**	**No. of Patient put on Shorter Regimen**	**Cured**	**Compl eted**	**Failed**	**Died**	**Lost to Follow-up**	**Not Evaluat ed**	**Still Under Treat ment**	Success rate
2017	Q4	2	100 %	0 %	0 %	0 %	0 %	0 %	0 %	100 %
2018	Q1	155	72 %	1 %	1 %	14 %	11 %	2 %	0 %	73 %
2018	Q2	174	68 %	3 %	1 %	9 %	15 %	4 %	0 %	72 %
2018	Q3	247	74 %	4 %	4 %	7 %	8 %	3 %	1 %	78 %
2018	Q4	226	69 %	5 %	3 %	11 %	10 %	3 %	0 %	74 %
2019	Q1	169	76 %	6 %	3 %	6 %	4 %	4 %	1 %	82 %
2019	Q2	225	63 %	4 %	4 %	13 %	8 %	4 %	6 %	67 %
Treatment Outcome of FQ Resistant Patients										
Year	**Quarter**	**Patients put on LTR & were FQ Resistant**	**Cured**	**Compl eted**	**Failed**	**Died**	**Lost to Follow-up**	**Not Evaluat ed**	**Still Under Treat ment**	Success rate
2017	Q1	136	60 %	1 %	5 %	21 %	11 %	1 %	0 %	61 %
2017	Q2	151	64 %	1 %	7 %	19 %	5 %	4 %	0 %	65 %
2017	Q3	122	59 %	1 %	11 %	22 %	7 %	0 %	1 %	60 %
2017	Q4	125	59 %	1 %	7 %	22 %	8 %	2 %	0 %	60 %
2018	Q1	204	54 %	3 %	11 %	21 %	5 %	3 %	1 %	57 %
2018	Q2	174	59 %	3 %	10 %	14 %	5 %	3 %	6 %	62 %
Treatment Outcome of FQ Sensitive Patients (on LTR)										
Year	**Quarter**	**Patients put on LTR & were FQ Sensitive**	**Cured**	**Compl eted**	**Failed**	**Died**	**Lost to Follow-up**	**Not Evaluat ed**	**Still Under Treat ment**	Success rate
2017	Q1	208	74 %	3 %	1 %	10 %	10 %	3 %	0 %	77 %
2017	Q2	190	65 %	4 %	3 %	14 %	12 %	2 %	0 %	69 %
2017	Q3	245	67 %	1 %	5 %	12 %	13 %	2 %	0 %	68 %
2017	Q4	195	63 %	4 %	1 %	22 %	9 %	2 %	1 %	66 %
2018	Q1	360	63 %	5 %	4 %	12 %	13 %	2 %	1 %	68 %
2018	Q2	270	62 %	6 %	5 %	15 %	6 %	2 %	3 %	68 %
Treatment Outcome of FQ Unknown Patients (were not some of them started on STR?)										

Year	Quarter	Patients put on LTR & their FQ Status was unknown	Cured	Completed	Failed	Died	Lost to Follow-up	Not Evaluated	Still Under Treatment	Success rate
2017	Q1	162	59 %	1 %	2 %	17 %	7 %	1 %	0 %	60 %
2017	Q2	176	60 %	1 %	2 %	23 %	11 %	2 %	0 %	61 %
2017	Q3	218	57 %	3 %	4 %	24 %	8 %	4 %	0 %	61 %
2017	Q4	134	56 %	1 %	1 %	25 %	16 %	1 %	0 %	57 %
2018	Q1	129	50 %	9 %	0 %	19 %	19 %	3 %	0 %	59 %
2018	Q2	99	45 %	10 %	1 %	26 %	11 %	5 %	2 %	56 %
Treatment Outcome of FQ Unknown Patients (were not some of them started on STR?)										
Year	**Quarter**	**Patients put on LTR & their FQ Status was unknown**	**Cured**	**Completed**	**Failed**	**Died**	**Lost to Follow-up**	**Not Evaluated**	**Still Under Treatment**	Success rate
2017	Q1	162	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
2017	Q2	176	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
2017	Q3	218	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
2017	Q4	134	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
2018	Q1	848	61 %	4 %	5 %	15 %	12 %	2 %	1 %	65 %
2018	Q2	717	61 %	5 %	5 %	15 %	8 %	3 %	3 %	66 %
2019	Q3	1565	60,6 %	4,8 %	4,7 %	15,2 %	10,1 %	2,8 %	1,6 %	65,4 %

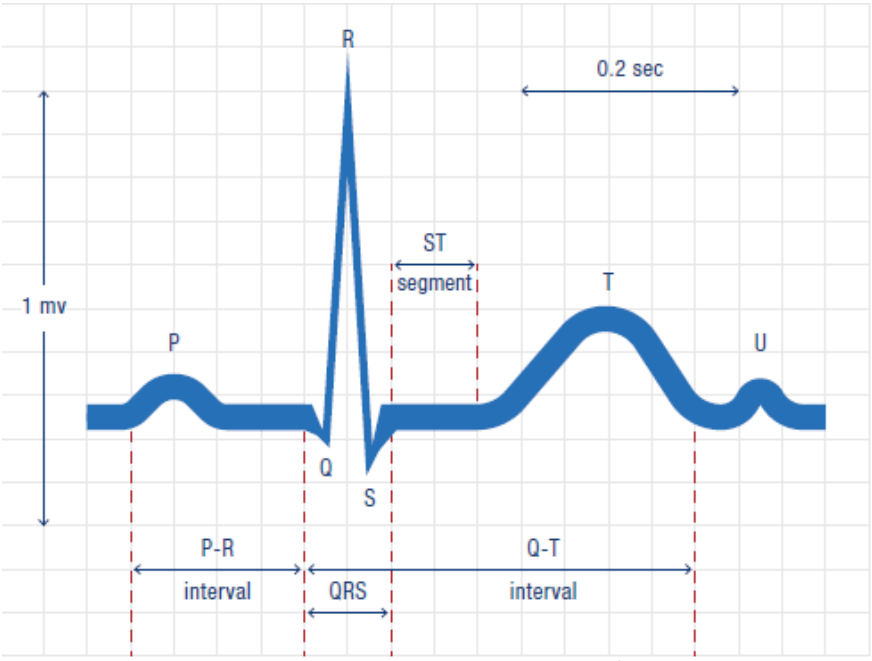
Annex 6: Recording and reporting of laboratory results from facilities with or without Xpert



Annex 7: **QT Interval and QTc: Definition, Measurement and Clinical Implications**

QT Interval:

- The QT interval is the ECG trace which begins at the start of the Q wave and terminates at the end of the T wave.
- The QT interval measures the time necessary for the ventricle to depolarize and repolarize.
- It is measured in seconds (s).



Characteristics and Features of the QT Interval:

- The QT interval varies in duration from one lead to another and may last up to 50 ms in healthy individuals. It is longer in V2 and V3 precordial leads.
- The QT interval can vary in the same individual by up to 75 ms on the same day.
- Several physiological conditions may affect the duration of the QT interval: sleep, the prone position, standing upright or orthostasis, etc.

Risk Factors for QT Lengthening:

- Female sex.
- Elderly people.
- Cardiac pathologies (hypertrophy, heart failure, ischemia etc.).
- Hypothyroidism.
- Hypokalemia, hypomagnesaemia, hypocalcaemia.
- Drugs that prolong and extend the QT interval (anti-tuberculosis drugs and drugs used to manage AEs: Mfx, Bdq, Dlm, Cfz and ondansetron at high dose).
- Bradycardia.
- Use of diuretics (furosemide and thiazides).
- Medical history of congenital long QT syndrome.
- HIV.

The QT interval is inversely proportional to heart rate.

• The QT interval becomes shorter in case of rapid heart rate.

• The QT interval lengthens in case of slow heart rate.

Why should the QT Interval be Corrected?

- The corrected QT interval (QTc) estimates the QT value at a heart rate of 60 beats per minute (bpm).
- This enables the comparison of QT values at different heart rates and improves the detection of patients with an increased risk of cardiac arrhythmias.
- The QT interval should not increase more than 60ms from the baseline.

What is the importance of the QTc?

- A prolongation of the QTc signifies that the heart muscle takes longer than normal to repolarize between contractions.
- Increased risk of arrhythmia (torsade de pointe) = syncope, sudden death.

What does QTc prolongation signify?

- Normal QTc is <450 ms in men and <470 ms in women.
- QTc is said to be prolonged when it reaches >500 ms in both men and women.

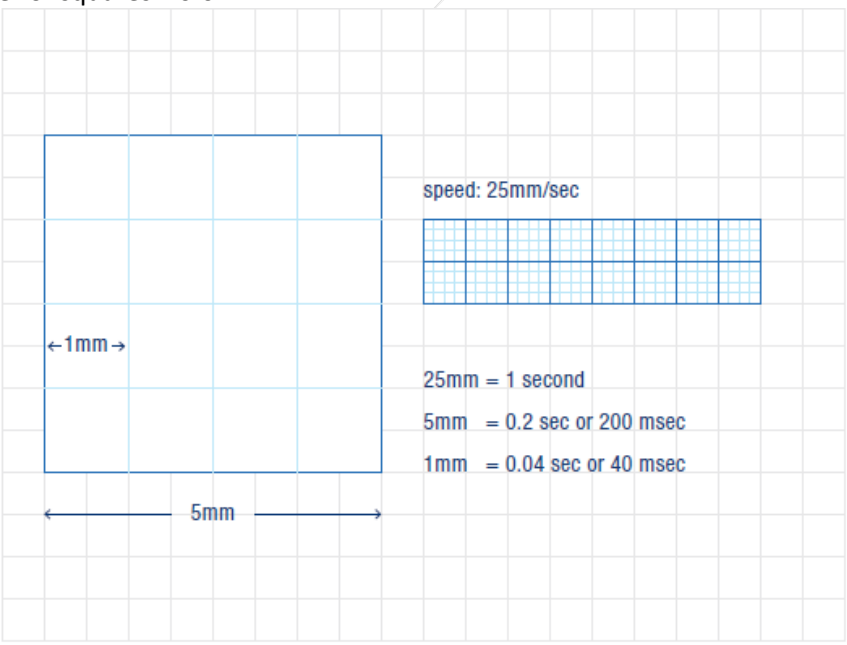
A prolonged QTc does not always indicate heart failure/cardiac disorder, but is a risk factor for arrhythmia (torsade de pointe) and may lead to syncope and sudden death. This is why some anti-tuberculosis drugs (Mfx, Cfz, Bdq, Dlm) are contraindicated in case of prolonged QTc.

Measurement of the QTc

Most ECG machines automatically measure the QT interval and the corrected QT (QTc). However, these measurements are not always reliable due to several reasons: algorithms used for the calculation differ among manufacturers; it is difficult to interpret the T and U waves; and the formula used is not always specified (Bazett's formula is widely used. It may over-correct or under-correct QTc according to heart rates). This is why it is important to know how to measure and calculate QTc manually.

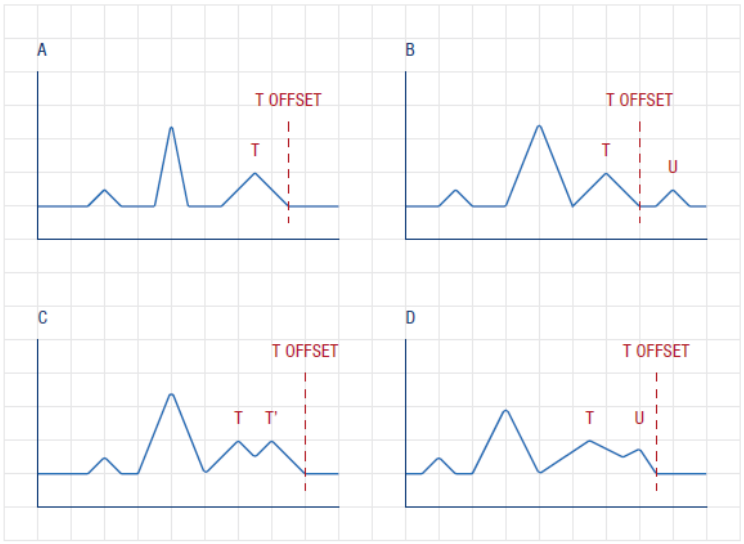
Step 1: measuring the QT interval

• Measure the QT interval in lead II, V5 or V6, as these show more clearly the end of the T wave.
• Several intervals (3–5) should be measured. The longest space should be taken into consideration.
• Measurement of the QT interval (in seconds): count the number of small squares from the beginning of the QRS complex up to the end of the T wave. Each square represents 0.04 s, if we assume the scroll speed to be 25 mm/s as usual.
.. 1 small square = 1 mm = 0.04 s (or 40 ms)
·· QT (s) = number of squares x 0.04



U waves

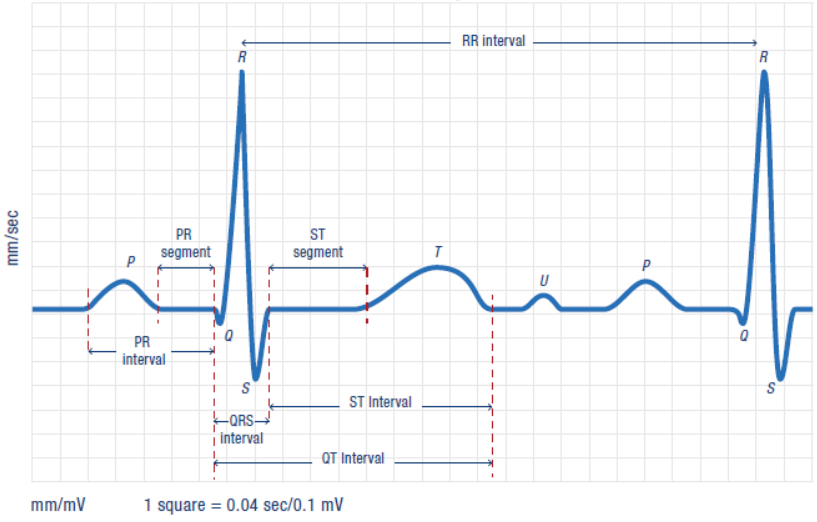
- Small U waves that are distinct from the T wave should not be measured; large U waves (>1 mm) that are merged with the T wave should be included in the QT measurement.
- Hypokalemia causes an apparent lengthening of the QT interval due to the merging of T and U waves, with the U waves evident in precordial leads.



A) T wave: measure QT interval at the end of the T wave.
B) Small U wave distinct from the T wave: measure the QT interval at the end of the T wave.
C) Dysphasic T wave (same morphology): measure QT interval at the end of the T' wave.
D) U wave merged with the T wave: measure QT interval at the end of the U wave.

Step 2: How to measure the R-R interval

- The R-R interval corresponds to the time elapsed between an R wave and the following one (duration of the R-R cycle).
- The R-R interval measures the time elapsed between one depolarization and another.
- It is measured in seconds (s).
- Several successive cycles (3 to 5) should be measured. The shortest interval should be taken into consideration.



- Measurement of the R-R interval (in seconds): count the number of small squares between the first R wave and the following one. Each square represents 0.04 seconds, assuming the chart scroll speed to be 25 mm/sec as usual.

·· 1 small square = 1 mm = 0.04 s (or 40 ms)
·· R-R (s) = number of small squares x 0.04

Step 3: How to calculate QTc

The Fridericia formula is reliable and used to calculate QT interval correction.

QTCF (s) = QT/3 RR

Annex- 8: INTERPERSONAL COMMUNICATION: (From Section-6, DR-TB Education & Counselling)

Interpersonal Communication is face to face verbal or non-verbal exchange of information and feelings between two or more people. It is a Two-way process of reaching mutual understanding.

Good communication is an essential part of good quality care. Many TB patients are poor, with very little money to use on health care. If the quality of care provided in our health facilities is of a low standard, patients may turn to unqualified healers WHICH may result in inadequate treatment.

Good communication is needed not only to inform patients of important messages about DR-TB and its treatment but it is also critical to encouraging patients to return for the next treatment visit, day after day and month after month.

PRINCIPLES OF EFFECTIVE COMMUNICATION

Always remember the acronym: **WELL**

W = welcome your patient

- ensure privacy and confidentiality
- greet the patient warmly (in a friendly manner)
- offer him/ her a seat
- ask his/ her name
- show empathy ("I understand how you feel")

E = encourage your patient to talk

- asking general questions ***"what is your (presenting) health complaint"***, ***"what are you concerned about"***
- nodding, agreeing or saying ***"Tell** me more about that"*

L = look at your patient

- make sure that your facial expression is warm and friendly
- maintain eye contact with your patient as they speak
- observe their feelings (as well as their general medical condition)

L = listen to your patient

- listen carefully to what your patient has to say and do not interrupt them
- show the patient that you are interested in what they are saying

Each DR-TB patient should receive the following information during the education sessions:

- What is TB and MDR-TB?
- TB transmission and ways of preventions
- What resistance is and how it develops?
- The main symptoms of TB & MDR-TB
- Reasons for performing a sputum examination for microscopy, Xpert MTB/RIF test and Culture& DST
- What is adequate duration of TB and DR-TB treatment?
- Why DOT is important?

Possible side-effects of treatment with second-line drugs and their effective management.

- Why it is important to complete treatment
- Consequences of non-adherence to treatment
- How MDR treatment is organized: time, place and frequency of TB drugs intake
- How the treatment plan is designed?
- How to live with DR-TB

Annex 9:

SOP: Strategy of Retrieval of non-adherent (missed follow up) and lost to Follow-up (default) Patients

One of the most important factors that are considered effective to enhance the patient adherence to long term MDR-TB treatment are patient education and early detection and management of adverse effects. It is the prime responsibility of MDR physician along with psychologist and treatment coordinator at PMDT site to provide early and complete patient education sessions informing about illness and personal role in treatment success in addition to close monitoring of ADRs and close monitoring.

In Pakistan the MDR-TB patient 2010 cohort analysis has shown about 7 % LTFU rate and it is also well known from studies that default rate is increased with the larger cohorts. Therefore, it is important to formulate a strategy for the follow up and retrieval of patients who are non-adherent or were lost to follow up MDR-TB patients. The experience has shown that with true efforts about 90% of the absconded patients are retrieved and continue or restart their treatment.

As per ambulatory model of care SOPs the patient will carry out weekly follow up visit to nearest BMU/DOTs center and monthly follow up visit to PMDT site along with treatment supporter. The immediate tracing mechanism should be initiated whenever the patient will miss routine follow up either at BMU/DOT center or at PMDT site.

1. Missed follow-up Strategy at BMU/DOTS Center
2. Missed follow-up Strategy at PMDT Site

1. Missed follow-up Strategy at BMU/DOTS Center

Staff responsible for reporting and initiating the procedure of follow up are; Medical officer, DOTS Facilitator, Treatment Supervisor and Treatment Supporter.

In case of a non-adherent or treatment interrupted patient who did not turn up on due date of weekly follow-up to the nearest DOTS Center, the following strategies at different levels should be adopted.

In case of one or more delay in the weekly visit, the BMU/DOTS Center staff takes measures that may include:

a) Sending a SMS message and/or calling the patient and/or treatment supporter to enquire about the reasons for delaying the visit and to encourage adherence (telephone contact numbers for patient and treatment supporter are recorded on DR-TB 01 kept at MDR-TB Clinic)

b) Visiting the home of patient to discuss with patient and Treatment Supporter (and patient's family) the reasons to delay and ways to avoid interruptions in future. The health staff keeps the discussion open to understand the reasons and feasible solution acceptable to the patient and his/her family. Be sensitive about the patient's confidentiality while making home visit.

2. AT PMDT Site Level

Staff responsible for reporting and initiating the procedure of reporting and follow-up are; MDR-TB Physician, Treatment Coordinator and Psychologist. The tracing mechanism must be initiated within 24 hours for hospitalized and 48 hours for patients on ambulatory care.

- If a patient does not visit the PMDT Site on due date of follow-up the Treatment Coordinator will report to MDR-TB Physician within 48 hours.
- The Treatment Coordinator will initiate the procedure to directly contact the patient, nearest contact person, treatment supporter by using the available contact details. Moreover, the method of sms/text will also be used.

- Medical Officer/HCW of the nearest health facility (BMU) will be contacted where patient is weekly visiting for follow-up. This is possible If treatment coordinator has already identified the nearest health facility and has the contact details of MO/HCW.
- If there is no response and treatment coordinator has already carried out home visit, in that case treatment coordinator will contact the person at nearest general store, Imam Masjid, Numberdar/Counselor and persons whom household contact screening is completed.
- If all above mentioned efforts did not work and patient has not turned up for follow-up visit then MDR-TB Physician will report such missed appointment cases to PTPs (Provincial MDR-TB Coordinator, Regional Coordinator of SRs, relevant NPOs and DTC) requesting their support.
- Consequently, Treatment Coordinator /Psychologist will arrange a home visit to the defaulted (lost to follow-up) patient, so that absconded patient can be retrieved and will use all ethical means and available resources to bring patient back at PMDT Site.
- MDR-TB Physician will ensure to add all missed doses (if > one week) at the end of treatment.

2.1. AT Provincial Level

The officers responsible for tracing the default (lost to follow-up patient) are; Provincial MDR-TB Coordinator, NPOs of relevant District, Regional Coordinator of SR.

- The Provincial MDR-TB Coordinator will send the enrolled patient data along with contact details and current status to all relevant DTC/DTOs on monthly basis.
- The Provincial MDR-TB Coordinator will make contact with the relevant NPO and DTC by e-mail and telephone to discuss the possibilities of retrieval of default (lost to follow-up) patients
- The NPO will further get in touch with DTC requesting and discussing the options to contact MO of nearest health facility LHS/LHW/DOTS Facilitator on the given address.
- The NPO and DTC will provide feedback to Provincial MDR-TB Coordinator about the status of retrieval of patient
- Provincial MDR-TB Coordinator will discuss the progress made for the retrieval of patients with MDR-TB Physician.
- Provincial MDR-TB Coordinator will keep in loop the national level and provincial SR during all communication and can ask for any additional support.

2.2 **At District Level**

At District level the responsible personnel to trace default (lost to follow-up) MDR-TB patients are DTC, MO/In-charge of the BMU/Health Facility, LHS and Treatment Supporter.

- The DTC/DTO will maintain and update the MDR-TB patient data on monthly basis for his district.
- The tracing mechanism will be conducted by the DTC/DTO as per available contact details and Treatment Supporter will be actively engaged.
- The DTC/DTO may himself contact/visit the patient or delegate duties to LHS/LHW of the area to visit patient and to see the family members, mentioning sensitivity of the matter and to use all ethical means and resources to send patient for follow-up.

- The DTC will present all cases in front of monthly District DR-TB monitoring meeting as discussed below.
- Once the patient is referred to township for ambulatory care and started visiting the nearest health facility for weekly follow-up, the MO/In-charge of the facility will be responsible for keeping patient adherent to treatment.
- The Treatment Supporter will inform the MO for any missed doses during that week and MO will insert note in treatment card.
- If a patient did not come for weekly follow-up visit at nearest health facility, the MO/In charge through HCW/paramedic will contact the patient and Treatment Supporter and arrange a home visit within 48 hours if required.
- The MO/In-charge of the facility where patient is carrying out weekly visit will play a key role in patient ongoing education, adherence to treatment and retrieval of absconded/default (lost to follow-up) patients.

At National TB Program Level:

- MDR-TB Unit at national level will develop strategy, provide technical assistance and communicate with Provincial TB Programs (PTPs) and implementing SRs whenever required.
- In a very remote area, lost to follow-up cases retrieval is difficult and will require special logistic support and MDR-TB unit at NTP as per available information will ask SR (Manager and Regional Coordinator) for provision of special logistic support so that the patient home visit can be carried out.

Once a patient has been traced, the situation should be addressed in a sympathetic, friendly and non-judgmental manner. Listen to the patient's reason for not coming to PMDT Site for follow-up, missing dose(s) or defaulting, and work with the patient and family to ensure continuation of treatment, while reminding the patient not to default again.

National level MDR-TB unit will facilitate and communicate with SRs/PTPs where additional support is required and will intervene where necessary

Annex 10: SLD-Demand form from PMDT Sites

S. #	Product Name	Opening Balance at Start of Reporting Quarter	Stocks received during the quarter	Consumption of Month 1	Consumption of Month 2	Consumption of Month 3	Total consumption of 3 Months	Closing Balance by End of Reporting Quarter	Demand for Next Quarter	Demand + 33% Buffer	Adjusted Quantity	Average Monthly Consumption	COMMENTS
1	Tab. Levofloxacin 250 mg						-	-	-	-	-		
2	Tab. Levofloxacin 500 mg						-	-	-	-	-		
3	Tab. Moxifloxacin 400 mg						-	-	-	-	-		
4	Tab. Bedaquilin						-	-	-	-	-		
5	Tab. Linezolid 600mg						-	-	-	-	-		
6	Tab. Clofazamine 100mg						-	-	-	-	-		
7	Cap. Cycloserine 250 mg						-	-	-	-	-		
8	Tab. Ethambutol 400 mg						-	-	-	-	-		
9	Tab Delamnid 50mg						-	-	-	-	-		
10	Tab. Pyrazinamide 400 mg						-	-	-	-	-		
11	Inj. Amikacin 500 mg						-	-	-	-	-		
12	Tab. Ethionamide 250 mg						-	-	-	-	-		
13	Sachet PAS 4 g *						-	-	-	-	-		
14	Tab Isoniazid 300mg						-	-	-	-	-		
15	Tab. Amoxicillin/Clavulanate						-	-	-	-	-		
16	Auto Disable Syringe 5ml						-	-	-	-	-		
17	Tab. Levofloxacin 100 mg (Paeds)						-	-	-	-	-		
18	Tab. Moxifloxacin 100 mg (Paeds)						-	-	-	-	-		
19	Tab. Clofazamine 50mg (Paeds)						-	-	-	-	-		
20	Cap. Cycloserine 125 mg (Paeds)						-	-	-	-	-		
21	Tab. Ethambutol 100 mg (Paeds)						-	-	-	-	-		
22	Tab Delamnid 50mg (Paeds)						-	-	-	-	-		
23	Tab. Pyrazinamide 100 mg (Paeds)						-	-	-	-	-		
24	Tab. Ethionamide 125 mg (Paeds)						-	-	-	-	-		
25	Tab Isoniazid 100mg (Paeds)						-	-	-	-	-		