The Union
International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

FIELD GUIDE FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

2018

The Union
International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

FIELD GUIDE FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

2018

Alberto Piubello, lead author

with contributions from
Nadia Aït-Khaled
José A. Caminero
Chen-Yuan Chiang
Riitta A. Dlodlo
Paula I. Fujiwara
Einar Heldal
Kobto G. Koura
Ignacio Monedero
Alberto Roggi
Valérie Schwoebel
Bassirou Souleymane
Arnaud Trébucq
Armand Van Deun

This publication was supported by the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association (RIT/JATA) and by Cooperative Agreement Number PS004641-04 funded by the U.S. Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of RIT/JATA and the U.S. Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

Editor International Union Against Tuberculosis and Lung Disease (The Union)
68, Boulevard Saint Michel, 75006 Paris, France

Suggested citation Piubello A, Aït-Khaled N, Caminero JA, Chiang C-Y, Dlodlo RA, Fujiwara PI, Heldal E, Koura KG, Monedero I, Roggi A, Schwoebel V, Souleymane B, Trébucq A, Van Deun A. Field Guide for the Management of Drug-Resistant Tuberculosis. Paris, France: International Union Against Tuberculosis and Lung Disease, 2018.

Photo Credits **Figure 2.1:** Institute of Tropical Medicine (ITM) Antwerp
Figure 2.2: Alberto Piubello
Figures 2.3 and 2.4: ITM Antwerp
Figure 8.1: Alberto Piubello
Figures 8.3 and 8.4: Alberto Piubello
Figure in Annex 5: Alberto Piubello

ISBN: 979-10-91287-20-3

Contents

Tables, Figures and Box

Tables

Figures

Box

Preface

This Field Guide for the Management of Drug-Resistant Tuberculosis is a practical tool intended to help health workers in the clinical and operational management of the disease with special focus on the introduction, implementation and management of the 9-month treatment regimen for multidrug-resistant tuberculosis.

The International Union Against Tuberculosis and Lung Disease (The Union) has been at the scientific forefront in combatting tuberculosis for nearly 100 years. We continue to engage in cutting-edge aspects of tuberculosis diagnosis, treatment and management today. In 2005, a dedicated unit for multidrug-resistant tuberculosis was set up.

The Union's Multidrug-Resistant Tuberculosis Programme provides pragmatic and hands-on support to countries through technical assistance and training courses.

Our expertise in the 9-month regimen is based on the studies carried out in partnership with the Damien Foundation, Brussels, and the Institute of Tropical Medicine, Antwerp, Belgium, in Bangladesh, Niger, Benin and Cameroon. Several significant lessons were also learned through the observational study of this regimen in nine Francophone African countries that The Union coordinated from 2013 to 2016.

It is gratifying to see that new evidence resulting in good treatment outcomes under programmatic conditions is generated by the national tuberculosis programmes in high-burden countries.

The Union hopes that readers will find this Field Guide, which supplements its Guide for the Clinical and Operational Management of Drug-Resistant Tuberculosis published in 2013, useful when caring for persons stricken with this potentially deadly form of tuberculosis.

Acknowledgments

The lead author has drawn numerous lessons on the management of drug-resistant tuberculosis through his long-standing collaboration with the National TB Programmes in Niger, Cameroon, West and Central Africa.

Warm thanks to Nathalie Guillerm for her careful review of this guide.

The Union gratefully acknowledges the contributions of the following organisations to the production of this Field Guide:

Damien Foundation, Brussels, Belgium

Institute of Tropical Medicine, Antwerp, Belgium.

Abbreviations and acronyms

AEs	adverse events
AFB	acid-fast bacilli
ALT	alanine transaminase
AST	aspartate transaminase
BMU	basic management unit
CPC	cetyl pyridinium chloride
DOT	directly observed treatment
DST	drug susceptibility testing
ECG	electrocardiogram
F1	failure of first treatment
F2	failure of retreatment
FQ	fluoroquinolone
FQ-R	fluoroquinolone-resistant
FQ-S	fluoroquinolone-susceptible
HIV	human immunodeficiency virus
LED	light-emitting diode
LPA	line-probe assay
LTFU	lost to follow-up
MGIT™	Mycobacteria Growth Indicator Tube
MTB	*Mycobacterium tuberculosis*
MDR-TB	multidrug-resistant tuberculosis
N	new case
NRL	National Reference Laboratory
NSAIDs	non-steroidal anti-inflammatory drugs
NTP	National Tuberculosis Programme
R1	relapse of first treatment
R2	relapse of retreatment
RR	rifampicin-resistant
RR-TB	rifampicin-resistant tuberculosis
RS	rifampicin-susceptible
RT	return to treatment (after LTFU)
SLI	second-line injectable
SLI-R	second-line injectable resistant
SLI-S	second-line injectable susceptible
TB	tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Anti-tuberculosis drug abbreviations

Am	Amikacin
Amx/Clv	Amoxicillin/Clavulanate
Bdq	Bedaquiline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
Gfx	Gatifloxacin
H	Isoniazid
Hh	Isoniazid high-dose
Imp	Imipenem
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
PAS	P-aminosalicylic Acid
Pto	Prothionamide
R	Rifampicin
S	Streptomycin
Trd	Terizidone
Z	Pyrazinamide

1 Introduction and definitions

1.1 Introduction

As *Mycobacterium tuberculosis* is an aerobic pathogen, its growth rate is highly affected by oxygen concentrations. In cavitary lesions of the lung parenchyma where oxygen concentration is high, *M. tuberculosis* reproduces rapidly.

M. tuberculosis resistance to anti-tuberculosis drugs is caused by spontaneous chromosomal mutations. The proportion of wild-type resistant mutants in an untreated *M. tuberculosis* population is usually very small. Treatment with anti-tuberculosis drugs imposes selection pressure on *M. tuberculosis* populations, resulting in a 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 anti-tuberculosis treatment. Primary resistance refers to patients infected with *M. tuberculosis* that is resistant to anti-tuberculosis drugs before treatment.

With a few exceptions, a mutation causes resistance to only one drug or group of drugs. Resistance to two or more drugs is caused by sequential mutations in different genes. Inappropriate regimens, use of lower-than-recommended doses, poor drug quality and poor adherence to treatment are commonly associated with the emergence of drug resistance.

1.2 Causes of resistance

Health care providers: inappropriate treatment	*Drugs: inadequate supply/quality*	*Patients: inadequate drug intake or treatment response*
Inappropriate guidelines	Poor quality	Lack of information
Non-adherence to guidelines	Unavailability of some drugs (stock outs)	Lack of means to adhere to treatment (transportation, food, etc.)
Absence of guidelines	Poor storage conditions	Social barriers
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 organised or funded TB control programmes		Substance abuse/dependency

Adapted from the Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, Switzerland: World Health Organization, 2014.

1.3 Definitions

- **Resistance among new patients:** resistance in patients who have never undergone anti-tuberculosis treatment or have taken anti-TB drugs for less than 1 month.

  These patients have been infected by other persons with resistant strains.

- **Resistance among retreated patients:** resistance in patients who have undergone anti-tuberculosis treatment for ≥1 month.

  This generally includes treatment failures, relapses or patients who return to treatment after being lost to follow-up (LTFU). These patients may have developed resistant bacilli during treatment, or may have been primarily infected or re-infected by other persons with resistant bacilli.

The incidence of drug-resistant TB has increased since the introduction of streptomycin, the first anti-tuberculosis drug. Cases of multidrug-resistant tuberculosis (MDR-TB) appeared after the widespread use of rifampicin from the 1970s onward. Extensively drug-resistant tuberculosis (XDR-TB) appeared following the misuse of second-line drugs. This indicates that the widespread use of a new drug may lead to the emergence of resistance to this drug. Resistance to drugs previously used may disappear from a population only very slowly.

Box 2.1 Case classification based on types of drug resistance
Cases are classified into the following categories based on the results of drug susceptibility testing (DST) performed on confirmed *M. tuberculosis* isolates.

- **Mono-resistant TB:** resistance to one first-line anti-TB drug only.
- **Polydrug-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. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

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 at least one of the three second-line injectables (SLIs) (amikacin, capreomycin and kanamycin), in addition to multidrug resistance.

Pre-extensively drug-resistant TB (pre-XDR-TB): *resistance to any FQ or to at least one of the three SLIs (amikacin, capreomycin and kanamycin), in addition to multidrug resistance.*

NB: Although this use of the definition for pre-XDR-TB is widespread, it is not officially recognised.

2 Detection

2.1 Patients' identification

Presumptive RR-TB cases are patients who are most at risk of having RR-TB. The following types of patients are considered a priority in low-income countries with low RR-TB prevalence.

- Smear-positive pulmonary TB patients who undergo treatment after failure (F1), or who have been successfully treated before and relapse (R1) and those who return to treatment after LTFU (RT) following first-line TB treatment for the first time. The proportion of R resistance is very high among people who fail treatment, but lower among people who relapse and in those who return to treatment after LTFU.
- Smear-positive pulmonary TB patients with poor outcomes on retreatment: retreatment failures (F2), relapses (R2) and patients who return to retreatment after LTFU (RT).
- Individuals with TB symptoms who are contacts of patients with known RR-TB.
- Patients from the private sector not integrated into the National Tuberculosis Programme (NTP) and about whom information on previous anti-tuberculosis treatment is lacking.

In settings with high RR-TB prevalence, all persons with TB should be tested for RR-TB.

Definitions in contact investigations

A contact of an infectious case (index case) is at high risk of infection and disease.

- *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).*

Symptomatic contacts of patients with RR-TB should undergo diagnostic tests for RR-TB without delay.

2.2 Diagnosis of rifampicin-resistant tuberculosis

No clinical or radiographic manifestations are specific for RR-TB. Diagnosis is based on the bacteriological identification of resistant strains.

It is essential to explain clearly to the patient how to produce good-quality sputum (deep inhalation, followed by coughing). A sputum sample consisting of saliva only is not useful.

Smear microscopy is the most accessible test for diagnosing TB. It detects the most infectious cases but cannot be used to detect drug-resistant TB. Nonetheless, it is recommended that smear microscopy be performed in addition to the Xpert test to assess bacillary load. This involves examining the patient's sputum smear using the Ziehl-Neelsen staining method or light emitting diode (LED) fluorescent microscopy with auramine staining. As the excretion of *M. tuberculosis* is intermittent, it is recommended that two smear microscopy tests be carried out.

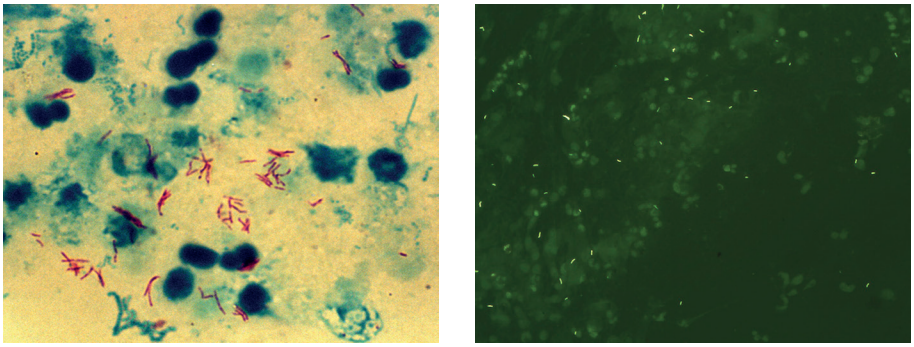


Figure 2.1 Smear microscopy using Ziehl-Neelsen (left) and auramine staining (right)

Genotypic or molecular methods used to detect drug-resistant TB (methods that detect target gene mutations that confer resistance to anti-tuberculosis drugs):

- The **Xpert® MTB/RIF** assay is an automated diagnostic test that identifies *M. tuberculosis* and detects R-resistance by amplifying nucleic acids. Results are obtained directly from sputum samples in <2 h. Xpert is a diagnostic test for drug-resistant TB. However, it is of no use during patient follow-up, as it detects the presence of genetic material, including dead bacilli that may be present even after the patient is cured. An Xpert result "MTB detected, rifampicin resistant/sensitive/indeterminate (whichever)" in a previously successfully treated patient does not confirm recurrent TB in the absence of clinical signs and symptoms and/or positive culture.

  Xpert testing is also recommended for the diagnosis of extra-pulmonary TB, although it may not be suitable for some types of extra-pulmonary samples. Samples from cerebrospinal fluid, lymph nodes and other tissues are suitable. However, the test has low sensitivity for pleural fluid, and data on its sensitivity in stools or urine samples are limited.

  The Xpert test provides the following six results: 1) "MTB not detected"; 2) "MTB detected" (high, average, low or very low) with 2a) "resistance to rifampicin detected" (i.e., rifampicin-resistant), 2b) "resistance to rifampicin not detected" (i.e., rifampicin-susceptible); 3) "indeterminate"; 4) "no result"; 5) "error"; or 6) "invalid result".

  The instrument needs to be recalibrated annually. It also needs a very stable electricity supply. A standard 2,000 W inverter and 12 V/100-400 Ah batteries provide power for over 8 hours to one four-module Xpert machine and a laptop (200 W required) in case of power cuts. These can be procured locally.

  The Xpert® MTB/RIF Ultra (Cepheid) shows significantly increased sensitivity with lower specificity than Xpert in the detection of *M. tuberculosis* in specimens with low bacillary load, particularly in smear-negative, culture-positive specimens, such as those from persons with HIV co-infection, in paediatric specimens and in extra-pulmonary specimens.

  The Xpert® Omni (Cepheid) is a completely portable device, closer to a point-of-care test.

- **Line-probe assay (LPA; GenoType MTBDRplus and GenoType MTBDRsl**; Hain Lifesciences, Nehren, Germany) is used to detect genetic mutations that render *M. tuberculosis* strains resistant to H, R (first-line LPA, FL-LPA), SLIs and FQs (second-line LPA, SL-LPA). SL-LPA is recommended for the detection of pre-XDR- and XDR-TB. This procedure takes 24–48 hours; however, in real life, turnaround times can be considerably longer. Moreover, it is very difficult to decentralise the LPA in low-resource countries.

Phenotypic methods (methods based in the detection of bacillary growth in culture media containing antibiotics):

- **Culture in solid medium** is more sensitive than automated culture in liquid medium in detecting R resistance; it is also less expensive and the risk of infection for laboratory staff is lower than that with liquid culture. Solid medium culture systems detect bacillary growth even when the number of bacilli is small and can be used for **drug susceptibility testing** (**DST**), which detects resistance to anti-tuberculosis drugs, including first-line drugs, such as rifampicin and isoniazid and second-line drugs, such as SLIs and FQs. It can be used to differentiate low- and high-level resistance to FQs. Tests for ethambutol, pyrazinamide, prothionamide, cycloserine and PAS are not reliable. Methods for testing bedaquiline, delamanid and linezolid have recently been validated.

  Bacillary growth is slow and entails long waiting periods (up to 2 months before a culture can be declared negative).

Figure 2.2 Xpert, LPA incubator and solid medium culture showing bacilli colonies

- **Liquid medium culture** in automated systems is based on the detection of oxygen consumption by bacilli. The MGIT™ (Mycobacteria Growth Indicator Tube; BD, Sparks, MD, USA) system comprises test tubes supplemented with solutions containing critical concentrations of anti-tuberculosis agents that are inoculated with sample strains and control test tubes without anti-tuberculosis drugs, which are read daily for fluorescence emission of an indicator sensitive to oxygen concentrations at the bottom of the tube. A strain is said to be resistant if the fluorescence reading is positive within 2 days after the control tube turns positive. Results are generally obtained in 3–14 days (but may sometimes take up to 6 weeks) and are calibrated against results obtained using the 1% proportion method. Methods for testing bedaquiline, delamanid and clofazimine have recently been validated.

  This method requires a biosafety level 3 containment laboratory.

Figure 2.3 MGIT™ system (left) and a test tube showing Mycobacterium growth (right).

The interpretation of anomalous or discordant results is presented in Annex 1.

Chest X-ray does not confirm the presence of RR-TB; however, the chest X-ray is a sensitive test and particularly useful for diagnosing TB in children and HIV-positive persons, who often have smear-negative TB. Whenever possible, it should be used in combination with Xpert in these populations.

2.3 Diagnostic procedure

- Use Xpert test for diagnosis in presumptive RR-TB patients.

Confirming R resistance by repeating Xpert test is not necessary in persons with presumptive RR-TB, as the Xpert test has a very high positive predictive value, and the high prevalence of R resistance in this group.

If screening is carried out among low-risk populations, such as new patients in settings with low RR-TB prevalence, results should be confirmed using a second Xpert test on another sample, as the positive predictive value is relatively low in this case. Although the system yields RR-TB results of high specificity, false-resistant results may be obtained due, for example, to laboratory errors. These occur more frequently in specimens with very few bacilli.

Repeat Xpert testing using another, good-quality sputum specimen; the second result should be considered definitive.

Sample preparation: a Falcon® (Fisher Scientific, Hampton, NH, USA) tube is prepared with alcohol to which sputum is added. The prepared solution is then sent to an Xpert-equipped laboratory.

To ensure inactivation of the bacilli, the final concentration of ethanol should be approximately 70%. For this, 2 volumes of ethanol at 95% should be added to 1 volume of sputum.

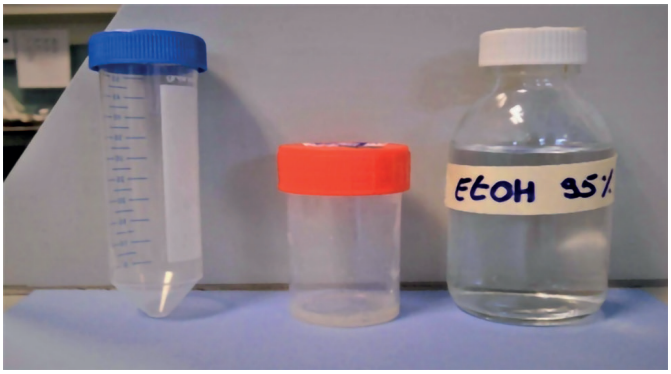


Figure 2.4 Falcon® tube + 1 volume of sputum + 2 volumes of 95% ethanol

See Annex 2 for the preparation, transportation and processing of sputum samples.

2.3.1 Sample processing

- Health care workers at the basic management unit (BMU) identify patients with presumptive RR-TB.
- Health care workers send samples prepared in alcohol to the laboratory technician, who is the focal person at the nearest Xpert site, with an Xpert test request form.
- The focal person at the Xpert site returns the form with the result to the BMU and communicates the result by telephone or other means to the appropriate person.
- If the Xpert machine is equipped with connective software, the result is sent automatically to the prescribing person and the NTP by internet or text message (sms).
- If R resistance is detected:
  - Whenever possible, the MDR-TB Unit sends a sample to the National Reference Laboratory (NRL) for second-line LPA.
  - Another Falcon® tube containing sputum pre-treated with cetyl pyridinium chloride (CPC) is sent to the NRL for culture in solid medium and DST as per the procedure described in Annex 2. Fresh refrigerated sputa should be sent for culture in liquid medium.

2.3.2 Patient management

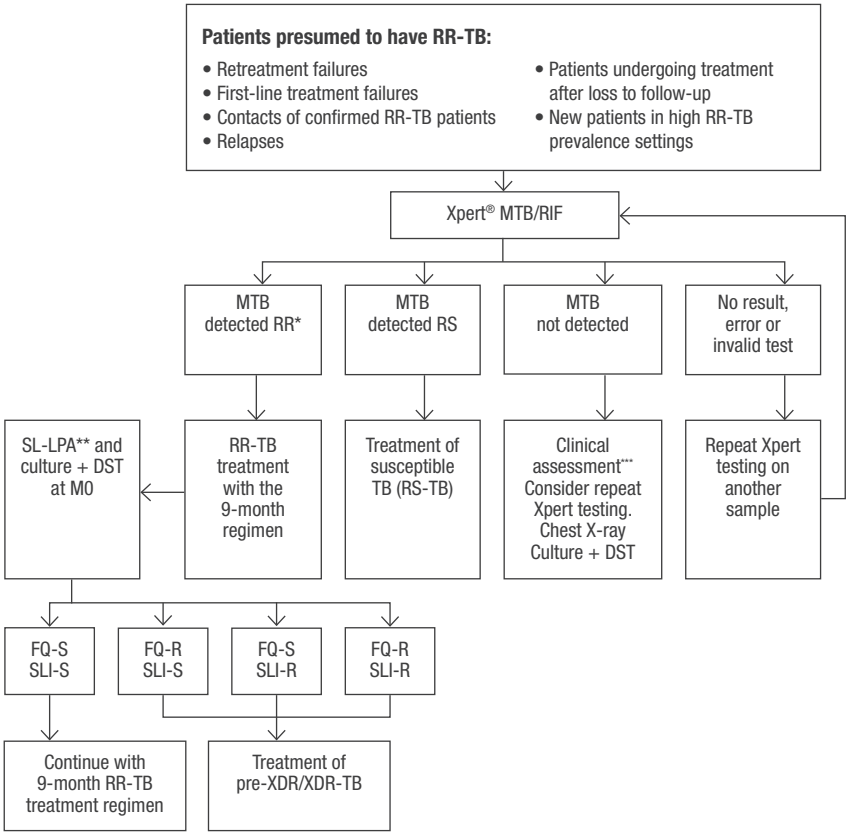
- If R resistance is not detected, the patient is treated at the BMU using the standard treatment regimen for rifampicin-susceptible TB according to national guidelines; DOT should be administered.
- If R resistance is detected, the patient is referred to the MDR-TB Unit. The BMU TB officer fills out a referral form and immediately notifies the MDR-TB Unit by telephone. The officer indicates the scheduled arrival time of the patient.
- The MDR-TB Unit defrays the costs of the patients' transportation in advance or reimburses them on arrival.
- When the patient arrives at the MDR-TB Unit, the latter confirms this by telephone to the BMU of origin.
- If the patient does not reach the MDR-TB Unit, the latter informs the BMU of origin, which then conducts a search for the patient.
- If the patient has never undergone second-line treatment before, the MDR-TB Unit registers the information on his/her patient record and starts the short-course treatment.

- If the patient has already undergone second-line treatment before, or if he/she is a contact of a person with pre-XDR-/XDR-TB, or in settings with high prevalence of resistance to FQs and/or SLIs, it will be necessary to await SL-LPA results to decide the most appropriate treatment regimen. If SL-LPA is not available or results are delayed, an individualised treatment based on previous use of second-line drugs or on the resistance pattern of the contact case should be started.
- The treatment regimen is changed in case resistance to FQs and/or SLIs is detected on the SL-LPA test or on phenotype DST.

Summary:

- *Perform Xpert testing in all persons with smear-positive TB who have already undergone anti-tuberculosis treatment and in all contacts of confirmed RR-TB patients on a priority basis.*
- *If R resistance is detected in a new case in settings with low RR prevalence, repeat Xpert test on another sample. If resistance is confirmed, treat the patient as having RR-TB.*
- *If R resistance is not detected, initiate treatment for rifampicin susceptible TB, with strict monitoring of clinical progress and especially changes in smear positivity.*
- *Immediately start treatment in all patients found to have RR-TB and who have not received second-line drugs in the past.*
- *Perform contact investigation, particularly among children, persons who are HIV-positive and other immunosuppressed individuals.*
- *Send a sample to the laboratory for SL-LPA test and send for culture with DST to identify pre-XDR- and XDR-TB cases.*
- *Change to an appropriate treatment regimen (pre-XDR- and XDR-TB) if resistance to FQs and/or SLIs is detected or suspected.*

Diagnostic algorithm for drug-resistant tuberculosis



*If the patient is at low risk for RR-TB, consider the possibility of a clerical error. In such cases, it is advised to repeat the Xpert test before starting treatment. In case of discordant results, start a treatment based on the second test result.

**SL-LPA should be performed whenever possible if the patient has already undergone treatment with second-line drugs or in settings with high prevalence of resistance to FQs and/or SLIs. If SL-LPA is not available, regimen to be designed based on previous use of second-line drugs.

***Complete clinical assessment (general conditions, presence of lymphadenopathy) and chest X-ray. Prescribe a 10 day course of non-specific antibiotic treatment (excluding quinolones) and reassess after 10 days with particular attention to children and patients co-infected with HIV.

Note: the 9-month regimen should be changed to an individualised regimen if the patient meets the criteria for failure and in case of proven SLI-R and/or FQ-R on LPA and/or culture + DST.

3 Regimen for RR-TB and treatment follow-up

This regimen applies to RR-TB patients with no previous history of second-line drugs use and with strains that are susceptible to FQs and to SLIs.

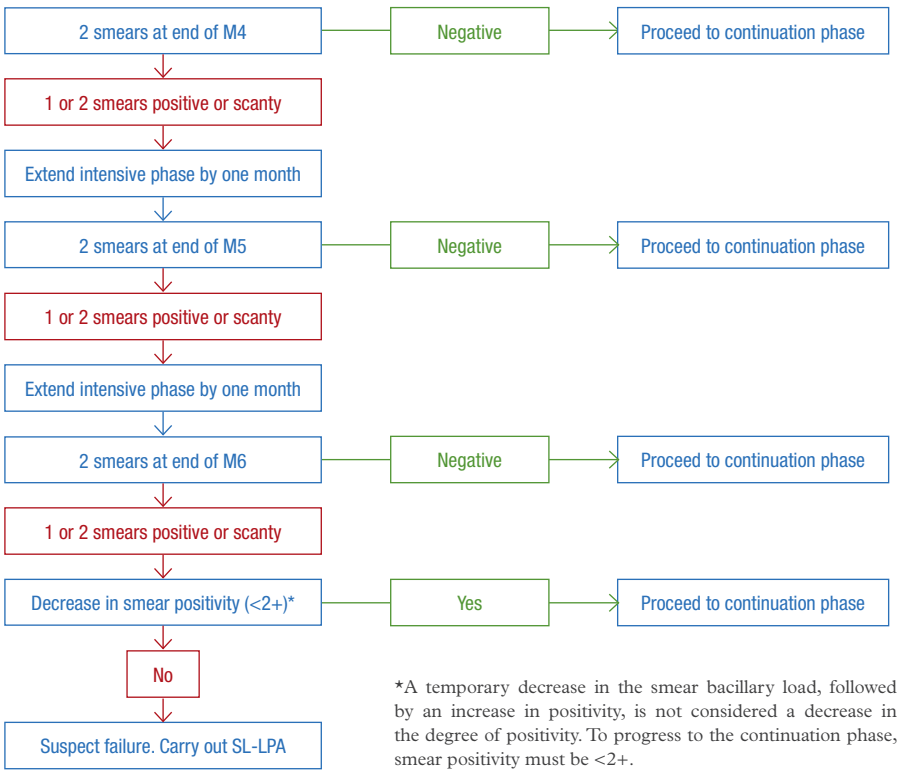
The short treatment regimen was developed to be used in settings with a low level of resistance to second-line drugs. It has the clear advantage of being short, only 9-11 months and inexpensive. The fact that it is standardized is also a significant advantage.

Although gatifloxacin is currently not available internationally, certain national authorities and partners are making efforts to bring this drug back to market. Data from Bangladesh, Cameroon and Niger suggest that the use of high-dose gatifloxacin leads to very low failure and relapse rates in settings with a low to medium FQ resistance.

The duration of the regimen is from 9 to 11 months, with an intensive phase of 4 to 6 months followed by a continuation phase of a fixed duration of 5 months.

Regimen: 4-6 Am – Mfx (or Gfx) – Pto – Hh – Cfz – E – Z/5 Mfx (or Gfx) – Cfz – E – Z

The continuation phase begins at the start of M5 if two sputum smears at the end of M4 are negative. If a smear is positive at the end of M4, take the following action:



*A temporary decrease in the smear bacillary load, followed by an increase in positivity, is not considered a decrease in the degree of positivity. To progress to the continuation phase, smear positivity must be <2+.

The duration of the continuation phase remains fixed at 5 months, regardless of the duration of the intensive phase.

If there is no bacteriological response and the patient's clinical status does not improve by M6, there is high suspicion of failure. An LPA test should be requested.

At M6 or later, if culture remains positive or reverts to positive after conversion or, in the absence of culture results, if two consecutive smears are ≥2+ positive and the patient does not show clinical improvement, the patient's treatment outcome is categorised as "failure", an LPA test is requested, the standardised regimen is discontinued and an individualised treatment regimen started.

Inclusion criteria
This regimen can be administered to adults and children with:

- pulmonary TB.
- extra-pulmonary TB, except meningeal or central nervous TB.

N.B. A specific regimen for children with weight <30 kg is described in detail below.

Exclusion criteria
This regimen does not apply to:

- Failures, relapses or patients on treatment after loss to follow-up to a second-line regimen, even if the LPA indicates susceptibility to FQs and SLIs or remains inconclusive.
- Patients with resistance to FQs and/or to SLIs.

RR-TB/HIV co-infection
RR-TB patients with HIV co-infection should receive antiretrovirals according to national guidelines with no modifications to the RR-TB regimen.

Drug dosage
Moxifloxacin or gatifloxacin is used at high dose. Preference should be given to gatifloxacin, if available, as it is more effective in preventing failures and relapses.

Prothionamide may be replaced by ethionamide.

Drug dosage according to patient weight is presented in Tables 3.1 (adults) and 3.2 (children).

Table 3.1 Daily drug dosage by patient weight (adults and children ≥30 kg)

	Weight (kg)			
Drug	*30-39*	*40-54*	*55-70*	*>70*
Amikacin§ (1 g) IM	0.5 g	0.75 g	1 g	1 g
Clofazimine (50 mg) cps	1			
Clofazimine (100 mg) cps		1	1	1
Ethambutol (400 mg) tab	1.5	2	3	3.5
Gatifloxacin (400 mg) tab	1	1.5	2	2
Isoniazid (300 mg) tab	1	1.5	2	2
Moxifloxacin (400 mg) tab	1	1.5	2	2
Prothionamide (250 mg) tab	2	2	3	4
Pyrazinamide (400 mg) tab	2	3	4	5

§ Patients aged ≥60 years should receive a maximum dose of 750 mg per day. Am should be administered intermittently (3 times per week) if the intensive phase is prolonged.

NB: Dosage to be adapted to the weight noted at each check-up visit.

Note on intermittent use of amikacin: as there is a substantial exposure to aminoglycosides due to long tissue/plasma half-life, dosing strategies that ensure less accumulation of an injectable agent in the body would be less toxic and daily dosing might not be necessary.

The use of amikacin 3 times/week at higher doses (25-30 mg/kg) may be considered as a good alternative to reduce toxicity.

Higher doses would limit toxicity if the duration of drug administration is not very long, as in the case of the short-course treatment regimen; bacilli would be killed for several days after exposure, thus justifying intermittent doses from the start.

As evidence for it is lacking, this strategy may be considered with careful monitoring.

Children weighing <30 kg

Consider replacing moxifloxacin or gatifloxacin by levofloxacin in small children. Moxifloxacin tablets may pose problems due to their bitter taste. Moreover, the tablets are not scored and syrup is unavailable in many settings.

Because hearing loss has a significant impact on young children developing language skills, a careful monitoring with audiometry is recommended if the injectable is used.

Although evidence is lacking, a treatment without injectable would be advantageous for children. Consider replacing the injectable with delamanid and ensure careful monitoring. Linezolid is effective but more toxic.

Table 3.2 Daily drug dosage by patient weight (children)

	Weight (kg)						
Drug	*3-4.9*	*5-7.9*	*8-9.9*	*10-12.9*	*13-17.9*	*18-23.9*	*24-29.9*
Amikacin (1 g) IM°	15-30 mg/kg						
Clofazimine (50 mg) cps	1#	1*	1*	1	1	1	
Clofazimine (100 mg) cps							1
Ethambutol (400 mg) tab	0.25	0.25	0.5	0.5	0.75	1	1.5
Gatifloxacin (400 mg) tab				0.25	0.25	0.5	0.5
Isoniazid (100 mg) tab	0.5	1	1	1.5	2	3	3
Levofloxacin (250 mg) tab°°	0.25	0.5	0.75	1	1.25	1.5	2
Moxifloxacin (400 mg) tab				0.25	0.25	0.5	0.5
Prothionamide (250 mg) tab	0.25	0.5	0.5	1	1	1.5	2
Pyrazinamide (400 mg) tab	0.25	0.5	0.75	1	1.5	2	2.5

#Twice a week. *Thrice a week.

°Note on amikacin: calculate the lowest and highest dose according to the child's weight category. Choose the dose closest to the higher dose, e.g., for a child weighing 7.9 kg: if 15 mg/kg x 7.9 kg = 118.5 mg; if 30 mg/kg x 7.9 kg = 237 mg. Therefore, dose to be administered: 200 mg.

°°Note on levofloxacin: doses 15-20 mg/kg. Consider to split levofloxacin into 2 doses (morning and evening) in children ≤ 5 years.

NB: Dosage to be adapted to the weight noted at each check-up visit.

Children and adults on treatment can continue drinking and eating dairy products as there is no interaction between milk products and FQ absorption.

Initial assessment and treatment follow-up

The initial assessment comprises a medical examination, sputum smear microscopy, Xpert testing, SL-LPA (if available), culture and DST for first-line (H and R) and second-line (FQs and SLIs) anti-tuberculosis drugs, chest X-ray, audiogram, blood tests (creatinine, potassium, glucose, transaminase, blood cell count), pregnancy test for women of childbearing age and HIV testing. An electrocardiogram (ECG) should be performed and repeated a week after treatment initiation.

As in any potentially life-saving situation, treatment for drug-resistant TB should not be withheld from a patient due to a lack of full DST capacity.

Bacteriological follow-up consists of monthly smear microscopy. At the end of the intensive phase (generally at M4, M5 or M6 if the intensive phase is prolonged), two sputum samples should be subjected to smear testing. Culture should be performed at M2, M4, M6 and M9 (at M10 or M11 if the intensive phase has been prolonged). Follow-up after cure using smear and culture is performed at M15 and M21.

The frequency of clinical and laboratory examinations is described in Table 3.3. The frequency of examinations will be modified in case of adverse events and according to the clinical condition of the patient.

Modified short treatment regimens

There is currently no evidence on the effect of replacing any of the agents in the short regimen with alternative ones.

Any change of an agent in the standardized regimen should be done under operational research conditions.

Possible replacement agents include:

- bedaquiline instead of quinolone;
- delamanid, linezolid or bedaquiline (in this order) instead of injectable.

Table 3.3 RR-TB treatment follow-up

	M0	*M1*	*M2*	*M3*	*M4*	*M5*	*M6*	*M7*	*M8*	*M9*	*(M10)*	*(M11)*	*M15*	*M21*
Clinical evaluation (with weight)	X	X	X	X	X	X	X	X	X	X	(X)	(X)	X	X
Sputum smear	X	X	X	X	XX	X(X)	X(X)	X	X	XX	(XX)	(XX)	X	X
Xpert	X													
LPA 2nd line	X													
Sputum culture	X		X		X		X			X	(X)	(X)	X	X
DST	X													
Chest X-ray	X									(X)	(X)	(X)		
Hemogram	X													
Audiogram	X	(X)	X	(X)	X	(X)	(X)							
Blood glucose	X		X		X		X		X		(X)	(X)		
ECG	XX*		X		X									
Serum creatinine	X		X		(X)	(X)	(X)							
K^+	X		X		(X)	(X)	(X)							
AST, ALT	X		X		(X)	(X)	(X)							
Pregnancy test	X													
HIV test	X													

*D0 and D7

Ensure follow-up and monitoring at M5 and/or M6 if the intensive phase is prolonged beyond 4 months.

(X): Test to be performed if necessary or if the intensive phase is prolonged beyond 4 months.

4 Management of pre-XDR- and XDR-TB cases and patients with contraindications to the short treatment regimen

4.1 Pre-XDR- and XDR-TB

A pre-XDR- and XDR-TB treatment regimen is based on at least four new drugs likely to be effective.

- A drug with high bactericidal and high sterilising activity, such as bedaquiline, to be administered throughout treatment duration. As a limited number of drugs with high bactericidal and sterilising activity is available, bedaquiline should be preserved for the treatment of patients with contraindications to the short treatment regimen, to maintain a cascade approach.
- A drug with high early bactericidal activity, such as linezolid, to protect Bdq and to prevent resistance amplification. Because of its toxicity, Lzd should only be used in the intensive phase and its use should be carefully evaluated if given throughout treatment. Possible alternatives are meropenem or imipenem/cilastatin plus amoxicillin/clavulanate. These need an implantable venous access device, which is problematic in most endemic settings. Another possible option is amikacin if still susceptible.
- A companion drug with bactericidal activity, such as delamanid, to protect the action of the other drugs and to prevent resistance amplification. Possible alternatives are meropenem or imipenem/cilastatin plus amoxicillin/clavulanate.
- A sterilising drug, such as clofazimine, to prevent relapse after treatment cessation. In case of resistance to clofazimine, cycloserine is an option. However, its low sterilising activity must be taken into account. Pyrazinamide may be added because of its sterilising activity.
- High-dose isoniazid should also be added in the intensive phase for its bactericidal properties, except in case of confirmed high H resistance (mainly double katG and inhA mutations or katG deletion).

Fluoroquinolone use may be considered in case of proven susceptibility; however, the FQ in question should not be considered as one of the effective drugs in such cases. As this regimen includes several drugs, such as bedaquiline, clofazimine and delamanid, likely to prolong the QTc interval, the use of moxifloxacin is problematic. Gatifloxacin may be considered.

Prolonged use of bedaquiline with concomitant use of delamanid is considered off-label, as both drugs have been registered to be used for a maximum duration of 24 weeks. Data on the simultaneous use of the two drugs in the same patient remain limited, but the use of the two drugs have proved effective and safe to date. Nevertheless, the risk of creating additional drug resistance with a weak regimen is real and the proposed approach seems justified.

An all oral individualised regimen should be preferred whenever possible.

As an example, a regimen may be composed as follows: Bdq-Lzd-Hh-Dlm-Cfz-Z for a total duration of 18-20 months. The duration and composition of the intensive phase will depend on smear/culture conversion and drug toxicity.

Table 4.1 Daily drug dosage by patient weight in adults

	Weight (kg)			
Drug	*30-39*	*40-54*	*55-70*	*>70*
Amikacin§ (1 g) IM	0.5 g	0.75 g	1 g	1 g
Amoxicillin/clavulanate 1 g tab	1 g/8-12 h			
Bedaquiline (100 mg) tab	4 tablets per day for 2 weeks, followed by 2 tablets 3 times/week			
Clofazimine (50 mg) cps	1			
Clofazimine (100 mg) cps		1	1	1
Cycloserine (250 mg) tab	2	2	3	3
Delamanid (50 mg) tab	2 tab two times a day			
Imipenem/Cilastatin (1 g/1 g) IV	1 g/12 h (dosed on the imipenem component)			
Isoniazid (300 mg) tab	1	1.5	2	2
Linezolid (600 mg) tab	1	1	1	1
Meropenem (1 g) IV	1 g/8 h			
PAS (PASER 4 g) pack	1/12 h	1/12 h	1/12 h	1/8 h
Pyrazinamide (400 mg) tab	2	3	4	5

§Patients aged ≥60 years should receive a maximum of 750 mg per day.

Table 4.2 Daily drug dosage by patient weight in children

	Weight (kg)						
Drug	*3-4.9*	*5-7.9*	*8-9.9*	*10-12.9*	*13-17.9*	*18-23.9*	*24-29.9*
Amikacin (1 g) IM°	15-30 mg/kg						
Amoxicillin/clavulanate (100 mg/ml +12.5 mg/ml) syrup	40 mg/kg/12 h						
Amoxicillin/clavulanate (825 mg/125 mg) tab						1/12 h	1/12 h
Bedaquiline (100 mg) tab	See note below						
Clofazimine (50 mg) cps	1#	1*	1*	1	1	1	
Clofazimine (100 mg) cps							1
Cycloserine (250 mg) tab	0.25	0.5	0.5	0.75	1	1.5	2
Delamanid (50 mg) tab	See note below						1/12 h
Isoniazid (100 mg) tab	0.5	1	1	1.5	2	3	3
Linezolid (100 mg/5 ml) syrup	See note below						
Linezolid (600 mg) tab							0.5
Meropenem (1 g) IV**	20-40 mg/kg/8 h						
PAS (PASER) 4 g packet***	0.25	0.25	0.5	0.75	1	1.25	1.5
Pyrazinamide (400 mg) tab	0.25	0.5	0.75	1	1.5	2	2.5

°Note on SLIs: Calculate the lowest and highest dose according to the child's weight category. Choose the dose closest to the higher dose, e.g., for a child weighing 7.9 kg: if 15 mg/kg x 7.9 kg = 118.5 mg; if 30 mg/kg x 7.9 kg = 237 mg. Therefore, dose to choose: 200 mg.

#Twice a week.*Thrice a week.

**Meropenem to be preferred as Cilastatin accumulation carries risk of seizures.

***Dose can be administered in 2–4 parts daily.

Note on the use of linezolid, bedaquiline and delamanid in children

Linezolid: due to its short half-life, children weighing <24 kg should be administered Lzd in daily syrup or suspension formulations. Seek expert opinion on a case by case basis when deciding. Crushing pills can be difficult and over or under dosage may occur. To avoid overdosing in children weighing 30–39 kg, consider using half a tablet (300 mg) daily.

Bedaquiline: its use in small children was under study at the time of going into press. The current recommended doses for children are as follows:

- Children weighing <33 kg: very limited experience (off-label use), seek expert opinion on a case by case basis when deciding.
- Children weighing >33 kg: use adult dosage, i.e., 400 mg daily for 14 days, followed by 200 mg three times weekly.
- Use for >24 weeks could be considered on a case-by-case basis if there is no alternative.

Delamanid: its use in small children was under study at the time of going into press. The current recommended doses for children are as follows:

- Children weighing <20 kg: very limited experience (off-label use), seek expert opinion on a case by case basis when deciding.
- Children weighing 20–34 kg: one 50 mg tablet twice daily.
- Children weighing >35 kg: use adult dosage, i.e., two 50 mg tablets twice daily.
- Use for >24 weeks could be considered on a case-by-case basis if there is no alternative.

4.2 Pregnant women and women of childbearing age

- Pregnancy is not a contraindication to treatment.
- The decision whether or not to treat should be based on an assessment of the risks and benefits for the mother and the fœtus.
- If treatment is deferred: high risk of serious worsening of the mother's general condition during pregnancy, increased risk of abortion, low birth weight and risk of disseminated TB for the baby.
- Inform patient of the risk of Am-related secondary ototoxicity and potential teratogenic risk for the fœtus. Consider replacing Am by Dlm or Bdq if Dlm is not available. Lzd is effective but more toxic.

RR-TB in pregnant women

- Risks:
  - For the mother:
    - Death, in case of no treatment.
    - Severe vomiting in the first trimester of pregnancy (Pto/Eto).
  - For the fœtus: potential teratogenic risk, ototoxicity (Am).
- Steps to take:
  - Immediate treatment initiation.
- Start short-course regimen. Consider replacing Am by Dlm or Bdq if Dlm is not available. Lzd is effective but more toxic.

RR-TB in women of childbearing age

- Do pregnancy test before treatment initiation.
- Advise against pregnancy during RR-TB treatment:
  - Encourage the use of contraceptives.
- During treatment follow-up visits:
  - Always enquire about amenorrhea.
  - Perform pregnancy test if needed.

4.3 Patients with kidney failure

Caution should be used in the administration of SLIs to patients with renal impairment. If creatinine clearance <90 ml/min, Am should be prescribed 2–3 times per week at 12–15 mg/kg; E and Z should be given three times per week. In case of creatinine clearance <60 ml/min despite dose reduction to 2-3 times/week, stop the injectable drug and replace it with Dlm or Lzd and continue E and Z three times per week.

Consider Bdq if Dlm is not available or if Lzd is contraindicated (severe anaemia, neuropathies etc.).

4.4 Patients with initial hearing loss

In patients with initial hearing loss, consider replacing Am by Dlm or Lzd if Dlm is not available, to prevent worsening of the hearing loss. The duration of the intensive phase remains unchanged. Consider Bdq if Dlm is not available, or if Lzd is contraindicated.

4.5 Patients with diabetes

Diabetic patients with drug-resistant TB may have worse treatment outcomes. Furthermore, the presence of diabetes may enhance adverse reactions to anti-tuberculosis drugs, particularly renal impairment and peripheral neuropathies. Diabetes should be closely monitored and treated throughout the duration of anti-tuberculosis treatment.

Nevertheless, none of the anti-tuberculosis drugs is contraindicated. Creatinine and potassium levels should be regularly monitored (weekly during M1, if possible), then at least once a month due to the adverse renal effects of SLIs.

5 Patient care and adherence

- It is vital to ensure an efficient **system of communication** between the Xpert-equipped laboratory and clinicians to rapidly obtain names of all patients with rifampicin resistance.
- Treatment should only be started after ensuring that an **adequate supply of drugs is available** to treat the patient until the end of the treatment course. Always set aside all the drugs required for a particular patient.
- **DOT is compulsory throughout the course of treatment** because the development of XDR-TB should be avoided at all costs and because AEs, particularly gastro-intestinal AEs, are frequent, as the number of tablets to swallow is very high. DOT should be planned and implemented in close consultation with the patient and his/her family so that a suitable treatment supporter can be identified and trained.
- All **AEs** should be clearly explained to patients and accurately documented in the patient treatment card. Patients should be referred to a physician if the nurse is unable to provide appropriate care.
- A **light meal** should be taken before giving any second-line medication.
- **Ambulatory treatment** from the start (or as early as possible) is more cost-effective than in-patient care and is likely to be more acceptable for the majority of patients. This will also prevent hospital-acquired infections.
- Some patients belonging to risk categories (children, pregnant women, those with comorbidities, etc.) or those who find it impossible to follow the daily ambulatory treatment as out-patients should be admitted in **hospital**.
- **Patient's preferences and barriers**, such as treatment options, distance to the health centre, travel costs, health centre opening times, incompatibilities with working hours etc., **should be evaluated** to adapt the service provided and to enhance adherence.
- **Social support** for the follow-up and monitoring of AEs, the costs incurred in daily transport in case of ambulatory care and nutritional support should be provided to patients.
- **The address of each patient, place of residence and telephone number** as well as the particulars and details of a guarantor should be noted in the patient's card. The patient's place of residence should be, wherever possible, visited at the start of treatment to ensure the accuracy of the information collected and to locate the house and investigate persons in close contact with the patient.
- Patients who fail to attend an appointment should be contacted the same or next day, if possible at first by telephone. If this is not possible, **a home visit** should be carried out to ascertain the reason for failure to attend the DOT session, prevent further irregularities and improve treatment adherence.

6 Identification and management of adverse events – pharmacovigilance

6.1 Identification and grading of adverse events

Adverse events (AEs) are more frequent in patients on second-line TB treatment than with first-line drugs and are the main cause of treatment interruption.

Good counselling at the beginning of the treatment and careful monitoring and management are the basis of patient adherence.

During the first baseline visit, comorbidities that are associated with a high risk of AEs, such as diabetes, kidney and liver failure, malnutrition, HIV infection, excessive alcohol and drug use, etc., should be identified and recorded.

The underlying causes of AEs should be identified and treated. AEs are classified according to their severity (Table 6.1).

Table 6.1 Grading of the severity of adverse events

Grade	*Description*
Grade 1: Mild	Mild or transient discomfort without limitation of normal daily activities; no medical intervention or corrective treatment required.
Grade 2: Moderate	Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.
Grade 3: Severe	Marked limitation of normal daily activities; medical intervention and corrective treatment required; possible hospitalisation.
Grade 4: Life-threatening or permanent injury	Extreme limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.

Ref: 2008 ANRS* scale for the gradation of the severity of adverse events in adults.

*Agence Nationale pour la Recherche sur le SIDA et les hépatites (National AIDS and Hepatitis Research Agency), Paris, France.

Reference values for testing for more frequent AEs and the classification of laboratory test results by AE severity for short treatment regimen and new drugs are described in detail in Annex 3.

Grade 1 AEs need only be noted in the patient's card, whereas Grade 2 AEs require medical intervention with ancillary drugs, of which the most frequently used are detailed in Table 6.2.

Table 6.2 Frequently used ancillary drugs

Therapeutic class	*Drugs*
Antidepressants	Amitriptyline
Antidiarrhoeals	Loperamide
Antiemetics	Metoclopramide (or metopimazine) and ondansetron
Antihistamines	Cetirizine (or diphenhydramine)
Antiulcer drugs	Cimetidine (or ranitidine) and omeprazole
Corticosteroids	Prednisolone, hydrocortisone
Non-steroidal anti-inflammatory drugs (NSAIDs)	Acetylsalicylic acid and ibuprofen
Vitamins and mineral supplements	Pyridoxine (vitamin B6). Potassium and magnesium.

These drugs should be stocked and be available at all times in TB treatment units where patients with drug-resistant TB are being treated.

Serious AEs (SAEs), which are either life-threatening or could cause permanent damage (degrees 3 and 4), should be managed by an experienced clinician who will identify the drug suspected, reduce dosage or discontinue its use and replace it with an equivalent drug if the drug needs to be definitively discontinued.

Changing a regimen drug should be considered only as a last resort after any attempt to manage AEs with ancillary drugs has failed.

6.2 Management of adverse events

6.2.1 Gastro-intestinal disorders

Nausea and vomiting
Suspected drugs: **Pto/Eto, PAS,** H, E, Z, Cfz, Bdq.

- Toxicity of the Pto/Eto on the gastric mucosa.
- Possible risk of hypokalaemia.

Treatment:

1 Rehydration using oral rehydration solution (ORS).

2 Recommend taking a light meal before medication.

3 Prescribe metoclopramide 10-20 mg 30 min before drug intake.

4 If vomiting persists, prescribe ondansetron 2–8 mg 30 min before drug intake.

5 Divide Pto/Eto dose into morning and evening provided DOT is ensured (dose-dependent effect; higher doses better tolerated by most patients in the evening).

6 For patients concerned about possible nausea, prescribe diazepam 5 mg 30 min before medication.

Gastritis
Suspected drugs: **Pto/Eto, PAS.**

Treatment:

1 Recommend taking a light meal before medication.

2 Absorption of FQs is reduced by drugs containing cations, such as magnesium and aluminium (and sucralfate) (high reduction); iron (moderate reduction); calcium, zinc (and multivitamins) (low reduction).

3 Prescribe omeprazole 20-40 mg in the evening (2 hours before or 3 hours after medication).

Diarrhoea
Suspected drugs: **PAS,** Pto/Eto.

Treatment:

1 Encourage patient to tolerate mild diarrhoea.

2 Encourage fluid intake.

3 Treat diarrhoea with no complications (no blood in the stools, no fever) with loperamide 4 mg, followed by 2 mg after each bowel movement up to a maximum of 10 mg in 24 h.

4 Check potassium levels and hydration status in case of severe diarrhoea.

Hepatotoxicity
Suspected drugs: **Z, H, Pto/Eto**, Bdq, PAS, Lzd, FQ (very rarely).

- Symptoms: nausea, vomiting, abdominal pain, jaundice.

Management:

1 Pay attention to medical history (viral hepatitis, HIV infection, alcohol use, etc).

2 If ALT, AST ≤5 times the upper limit of normal and there is no jaundice, continue treatment and treat nausea and vomiting.

3 If ALT, AST >5 times the upper limit of normal and/or jaundice (bilirubin>3 mg/dl), stop all drugs and assess the transaminases every week; if they return to 2 times the upper limit of normal, reintroduce the least hepatotoxic drugs (Am, E, Mfx, Cfz) and check transaminase levels. Then, reintroduce hepatotoxic drugs in the following order: Pto/Eto, H and Z and monitor transaminase levels every 3 days. Check transaminase values after introducing each drug.

4 If drug reintroduction leads to the return of hepatotoxicity, remove the culprit drug from the treatment and replace it by another if this is an essential drug. Do not replace H and Z.

5 Monitor transaminase levels monthly.

6.2.2 Kidney disorders

Nephrotoxicity
Suspected drugs: **Km, Am, Cm,** E, Z, Cs.

- Higher risk if intensive phase is prolonged.

Treatment:

1 Close monitoring of creatinine (and potassium) every week or every 2 weeks.

2 Adequate hydration.

3 If creatinine clearance <90 ml/min, prescribe Am 2-3 times per week at 12-15 mg/kg; give E and Z, 3 times/week. If creatinine clearance remains <60 ml/min despite dose reduction to 2-3 times/week, stop the injectable drug and replace it with Dlm or Lzd. Give E and Z, 3 times/week.

4 If Dlm is not available or if Lzd is contraindicated, consider Bdq.

NB: in case of increase in creatinine levels, severe malnutrition or advanced age, renal functions are determined by calculating creatinine clearance using the Cockroft-Gault formula:

$$\text{Cl Cr} = \frac{(140\text{-age})}{\text{Cr}} \times \text{Weight} \times k$$

- Cl Cr: estimation of the creatinine clearance in ml/min;
- Cr: creatinine levels in µmol/l;
- Age: age in years;
- Weight: in kg;
- k: coefficient (1.23 for men and 1.04 for women).

Note: Creatinine conversion from µmol/l to mg/dl: mg/dl = µmol/l / 88.4.

Table 6.3 Stages of kidney disease according to creatinine clearance levels

Stage of chronic kidney disease	*Creatinine clearance (ml/min)*	*Action on TB drugs*
Stage 1 Normal	≥90	
Stage 2 Mild	60–89	2-3 times per week
Stage 3 Moderate	30–59	Stop the injectable and switch to Dlm or Lzd or Bdq
Stage 4 Severe	15–29	
Stage 5 Terminal	<15	

Electrolyte imbalance

Suspected drugs: **Cm, Km, Am.**

- Hypokalaemia: K^+<3.5 mEq/l.
- Hypomagnesaemia: Mg^{2+}<1.5 mEq/l.
- Hypokalaemia may be refractory if the concurrent hypomagnesaemia is not corrected.
- Higher risk if intensive phase is prolonged.
- Vomiting, diarrhoea and diuretics may cause electrolyte imbalance.
- Risk of QTc prolongation (check ECG).
- Electrolyte imbalances are reversible upon discontinuation of the injectable drug (however, this might take weeks or months!).
- Hypokalaemia and hypomagnesaemia are often asymptomatic.
- Symptoms of moderate intensity: fatigue, myalgia, cramps, weakness of the lower limbs, somnolence, confusion.
- Symptoms associated with severe electrolyte loss: tetany, paralysis and severe arrhythmias.

Treatment:

1 Encourage dietary intake of potassium (bananas, oranges, tomatoes, chocolate …).

2 Check for signs of dehydration among patients with vomiting and diarrhoea. Start oral or IV rehydration.

3 Consider potassium supplementation: oral slow-release tablets of potassium chloride 1,200–3,600 mg daily in 2–3 divided doses (600 mg = 8 mEq).

4 In case of severe hypokalaemia: KCl IV: 10 mEq/h (10 mEq KCl will raise serum potassium by 0.1 mEq/l).

5 If potassium levels are low, check magnesium levels (if this is not possible, consider empirical treatment with magnesium in all cases of hypokalaemia with magnesium gluconate at 1,000 mg twice a day).

6 Prescribe spironolactone 25 mg/day in refractory cases.

7 Check ECG for QTc prolongation.

6.2.3 Neurological disorders

Peripheral neuropathy
Suspected drugs: **Lzd, Cs, H**, FQs, SLIs, Pto/Eto, E.

- Check for possible comorbidities: diabetes, HIV, alcohol abuse, hypothyroidism, malnutrition.
- No formal contraindications to anti-TB treatment in case of comorbidities.

Treatment:

1 Pyridoxine 100-200 mg/day (maximum dose 100 mg/day in pregnant women).

2 Amitriptyline 25-50 mg in the evening (maximum dose 150 mg/day in three doses).

3 Carbamazepine 100-400 mg x 2/day (follow-up and monitoring of transaminases).

Optic neuritis
Suspected drugs: **Lzd, E.**

- Serious, irreversible if medication is not immediately discontinued.
- Loss of colour vision (green colour first). Perform Ishihara test (table of colour discrimination). Ishihara tables are available on the web.

Treatment:

1 Immediate discontinuation of Lzd and/or E.

Seizures
Suspected drugs: **Cs**, H, FQs.

Treatment:

1 Discontinue Cs, the drug likeliest to be responsible.

2 Always check creatinine levels in patients with sudden onset of seizures. Compromised renal function may cause increased serum concentrations of Cs.

3 Begin anti-convulsive treatment (carbamazepine, phenytoin or valproic acid).

4 Replace Cs by Pto/Eto (or PAS) if not previously used in a failed regimen.

6.2.4 Osteoarticular disorders

Arthralgia
Suspected drugs: **Z**, FQs, Bdq.

Treatment:

- Prescribe NSAIDs: ibuprofen 600 mg 3 times/day.
- Rest the joint.
- Symptoms generally diminish with time and without any intervention.

Tendinitis (Achilles' tendon)
Suspected drugs: **FQs (all).**

Treatment:

1 Prescribe NSAIDs: ibuprofen 600 mg 2-3 times a day.

2 Rest the joint.

3 Tendon rupture is more probable among patients with diabetes and among the elderly, but rare among patients with MDR-TB.

4 If significant inflammation persists, discontinue FQ use and replace with Bdq.

6.2.5 Dermatological disorders

Itchiness, skin rashes and allergic reactions
Suspected drugs: **all**.

Steps to take:

1 Symptoms generally resolve spontaneously in the first few weeks.

2 In case of dryness of the skin, use moisturising cream.

3 Prescribe antihistamines (diphenhydramine 25–50 mg or cetirizine 5–10 mg before medication).

4 Prescribe corticosteroid ointments.

5 Prescribe oral prednisolone in low doses (10–20 mg/day) if there is no improvement.

6 Identify and discontinue the drug in question only in case of serious AEs (e.g., Stevens Johnson syndrome and Lyell's syndrome).

6.2.6 Thyroid disorders

Hypothyroidism
Suspected drugs: **Pto/Eto+PAS**, Pto/Eto, PAS.

- Reversible at the end of the treatment.
- If thyroid stimulating hormone (TSH) levels increase, assess symptoms of hypothyroidism.
- If TSH >1.5–2 times upper limit of normal, initiate treatment.

Treatment:

- Levothyroxine 100–150 μg/day in adults; 75–100 μg/day in young adults; 50 μg/day in elderly people (> 65 y); 25 μg in case of serious cardiovascular disease.
- Reassess TSH levels after 1–2 months and adjust levothyroxine dosage accordingly.

6.2.7 Metabolic disorders

Hypoglycaemia and hyperglycaemia
Suspected drugs: **Gfx**, Mfx.

- Reversible at the end of treatment.
- Good glucose control is important during treatment.
- Higher risk with Gfx than with Mfx.

Treatment:

1 Treat hypoglycaemia and hyperglycaemia as needed.
2 Stop Gfx, replace with Mfx and monitor glycaemia.

Lactic acidosis
Suspected drug: **Lzd**.

- Build-up of lactates in the body, which results in an excessively low pH in the blood.
- Consequence of mitochondrial toxicity.
- Monitor with blood test (arterial or venous).
- Symptoms: abdominal pain, nausea, vomiting, rapid deep breathing, general weakness.

Treatment:

1 Stop Lzd and replace with another drug with similar characteristics (e.g., imipenem or meropenem + clavulanic acid).

6.2.8 Haematological disorders

Bone marrow aplasia
Suspected drug: **Lzd**.

Treatment:

1 Discontinue Lzd immediately in case of severe medullar aplasia (Grade 3) of the white or red blood cells, or platelets.

2 Consider blood transfusion in case of severe anaemia.

3 Consider possible causes of haematological disorders unrelated to Lzd.

4 Reduce Lzd dosage (300 mg/day or 600 mg thrice a week instead of 600 mg/day) if the aplasia resolves and check complete blood count.

6.2.9 Psychiatric disorders

Depression
Suspected drugs and conditions: psychological and socio-economic conditions, Cs, H, FQs.

Treatment:

1 Assess psychological and socio-economic conditions.

2 Discontinue Cs, which is the drug most likely to cause depression.

3 Always check creatinine levels in patients with sudden onset of depression. Impaired renal functions can raise Cs serum concentrations.

4 If moderate or severe symptoms persist, initiate anti-depressant treatment with fluoxetine, amitriptyline or similar drugs. Do not administer these in conjunction with Lzd (risk of serotonin syndrome).

5 Replace Cs with Pto/Eto (or PAS) if not previously used in a failed drug regimen.

Psychosis
Suspected drugs: **Cs**, H, FQs.

Treatment:

1 Discontinue Cs, which is the drug most likely to be responsible.

2 Always check creatinine levels in patients with sudden onset of psychosis. Impaired renal function can raise Cs serum concentrations.

3 If moderate or severe symptoms persist, initiate antipsychotic treatment with haloperidol.

4 Replace Cs with Pto/Eto (or PAS) if not previously used in a failed regimen.

6.2.10 Cardiac disorders

QTc interval prolongation
Suspected drugs: **FQs**, **Bdq**, Dlm, Cfz.

- Mfx prolongs QTc more than Lfx and Gfx.

Treatment:

1 Repeat ECG and confirm QTc prolongation.

2 Take note of conditions such as diarrhoea, vomiting, use of diuretics, alcohol and ancillary drugs (ondansetron at high dose).

3 Check potassium, magnesium and calcium levels and maintain normal electrolyte levels (refer to electrolyte loss in the section on renal disorders).

4 If QTc <500 ms, continue Mfx or Bdq or Dlm and perform ECG once a week.

5 If QTc ≥500 ms, temporarily hold all drugs prolonging QT and replace Mfx with Gfx or high-dose Lfx (if Gfx is not available) after normalization.

6 If QTc still ≥500 ms, consider discontinuing Cfz and refer to cardiologist wherever possible.

7 If QTc still ≥500 ms, consider discontinuing Bdq and/or Dlm.

NB: Refer to Annex 4 for the definition, measurement and clinical implications of the QT interval.

6.2.11 Ototoxicity

Hearing loss
Suspected drugs: **Km, Am, Cm**.

- The frequencies between 500 Hz and 4,000 Hz are considered to be those of a normal conversation.
- The higher frequencies (4,000-8,000 Hz) are the first to be affected while the frequencies of the human voice come next.
- Hearing loss becomes perceptible for patients at a frequency <4,000 Hz when it reaches 25-30 dB.
- When patients mention hearing loss, there is already a severe degree of loss.
- Serial audiograms may help to detect and monitor patients at risk early.
- Hearing loss is irreversible.
- Caution: continuing with SLIs despite hearing loss almost invariably results in irreversible deafness.

Treatment:

1 If deterioration of hearing loss during the intensive phase (≥Grade 1), replace Am with Dlm or Lzd if Dlm is not available.

2 If Grade ≥1 hearing loss already at M0, consider the use of Dlm or Lzd instead of Am.

3 If Dlm is not available or if Lzd is contraindicated, consider Bdq.

4 Avoid furosemide and thiazides, which increase drug toxicity.

5 Hearing aids to be used if Grade 2 or 3 ototoxicity at treatment completion.

NB: Refer to Annex 5 for the description, measurement and clinical implications of audiometry.

6.3 Pharmacovigilance

All AEs should be recorded in the patient's card and in a database by type, degree and month of appearance.

Severe adverse events (Grades 3 and 4) should be notified to the NTP and the Pharmacovigilance Department of the Ministry of Health (see Annex 6, Adverse Events Reporting Form).

7 Registration, recording, reporting and drug management

7.1 Definitions

7.1.1 Case definitions based on previous treatment history

New case (N): patient who has never been treated for TB or who has taken anti-tuberculosis drugs for less than 1 month.

Failure (F1): patient who remains smear-positive at month 5 or later during primary treatment.

Retreatment failure (F2): patient who remains smear-positive at month 5 or later during retreatment.

Relapse (R1 and R2): patient who has undergone treatment for TB with the first-treatment regimen (R1) or retreatment (R2), has been declared "cured" or "treatment completed", but is again diagnosed with smear- or culture-positive TB.

Return to treatment (RT): smear-positive patient who returns to treatment after an interruption of >2 consecutive months (who had been declared "lost to follow-up").

Other (O): patient who belongs to none of the above categories.

7.1.2 RR-TB treatment outcome definitions

Treatment outcome definitions presented in this guide are those proposed by The Union for the short-course treatment regimen for RR-TB and are therefore adapted to its shorter duration.

Compared to previously recommended prolonged individualised regimens, the short-course regimen introduces several new features: the intensive phase is much shorter; criteria for switching from the intensive phase to the continuation phase are based on smear results; the total duration of regimen is short, which makes it more difficult to rely on culture results when taking decisions; the regimen is standardised and all drugs are essential and rarely replaced.

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 smear 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.

For longer regimens, the WHO current definitions (2013) are applied:

Cured: Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a].

Treatment completed: Treatment completed as recommended by the national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a].

Died: A patient who dies for any reason during the course of treatment.

Failure: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion[b] by the end of the intensive phase[a], or
- Bacteriological reversion[b] in the continuation phase after conversion[b] to negative, or
- Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or
- Adverse drug reactions.

Lost to follow-up: A patient whose treatment was interrupted for 2 consecutive months or more.

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.

[a] For failure, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Failure start to apply.

[b] The terms "conversion" and "reversion" of culture as used here are defined as follows:

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.

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 are found to be positive. For the purpose of defining Failure, reversion is considered only when it occurs in the continuation phase.

7.2 Recording and reporting forms

Request forms for smear microscopy (Form 6.1), Xpert test (Form 6.2), LPA, culture and DST (Form 6.3) as well as all the other reporting tools are provided in Annex 6.

A **laboratory register for patients tested using Xpert (Form 6.4a)** should be kept in each laboratory using an Excel type spreadsheet. The register should be used to identify and keep track of all RR-TB cases. This file should be updated regularly (at least once a week) and completed based on information received about patient management.

TB coordinators should ensure that Xpert results are entered in a timely manner in BMU TB registers and BMU quarterly reports, to monitor coverage of Xpert testing in previously treated and new TB patients.

The **laboratory register of confirmed RR-TB patients with treatment details (Form 6.4b)** should be used to assess the proportion of RR-TB patients started on treatment and should be kept regularly updated by MDR-TB Units. Both paper and electronic versions of the laboratory register should be maintained.

Paper-based **treatment cards of individual RR-TB patients (Form 6.5)** should be used to ensure follow-up.

The **RR-TB treatment register (Form 6.6)** should include all diagnosed RR-TB patients started on treatment.

A **RR-TB detection and treatment initiation report (Form 6.7)** should be made on a quarterly basis based on the laboratory register on confirmed RR-TB patients with treatment details and/or the BMU TB register. Based on the RR-TB register, a **report on second-line treatment results (Form 6.8)** should be filled out and completed on a quarterly basis.

If there are Serious AEs (Grades 3 and 4), the **Adverse Events Reporting Form (Form 6.9)** should be completed and sent to the Pharmacovigilance Department of the Ministry of Health. Any AE will be recorded in an electronic individual database, which should be updated with the annual analysis of each patient cohort.

7.3 Drug management

The central NTP team should quantify second-line drug requirements half-yearly based on the number of reported RR-TB cases, reported Xpert coverage, and planned expansion and projections for the number of RR- and pre-XDR/XDR-TB patients in the next 12 months. Drug requirements for these patients should then be calculated and current stocks subtracted to arrive at the quantity of drugs to be ordered. It is also important to monitor the expiry dates of the drugs in stock.

There is usually a delay of around 6–8 months from order to delivery; this needs to be taken into account in the calculations. A buffer stock of a minimum of 6 months should be maintained.

Drugs are generally distributed from the central level to MDR-TB units where treatment is started.

Second-line drugs are generally packaged in kits for individual patients for the entire duration of the short regimen, while for longer individualised regimens, drugs are usually sent periodically to prevent expiry.

The central unit should closely monitor stock levels and expiry dates in MDR-TB units and redistribute when needed.

8 Infection Control

Tuberculosis transmission occurs from person to person mainly by air, through infected droplets released into the environment by an infectious patient who has not been diagnosed and started on appropriate treatment.

Risk factors for TB transmission are linked to:

- The infectiousness of the patient (smear positivity, presence of cavitation, intensity and frequency of cough).
- Absence of treatment or non-supervised treatment.
- Individual and acquired predisposition: HIV, malnutrition, diabetes, children etc.

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.

Infection control measures are ranked in order of priority.

Table 8.1 Infection control measures by priority

Priority	*Type of measure*	*Objective*
First	Administrative control	Reduce exposure of all people within the area where there may be exposure to TB.
Second	Environmental control	Reduce concentration of infectious particles.
Third	Individual respiratory protection	Protect health personnel in areas where the concentration of particles cannot be reduced.

Administrative control measures are effective and essential; environmental control measures are more difficult to apply and more costly and respiratory control measures may not be useful without the application of the other two types of measures.

8.1 Administrative control measures

In the health care setting:

- 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.
- Sensitisation of staff, patients and their families, visitors.
- Monitoring for TB among health care workers involved in TB care.

At home:

- 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.

8.2 Environmental control measures

In order to reduce the number of infectious airborne droplets in health facilities, it is necessary to ensure good ventilation of waiting and consultation rooms and hospital wards.

Natural ventilation

Figure 8.1 Examples of natural ventilation in two MDR-TB units in Niger

- Open doors and windows to maximise 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.
- Adequate in tropical regions.

Mechanical ventilation

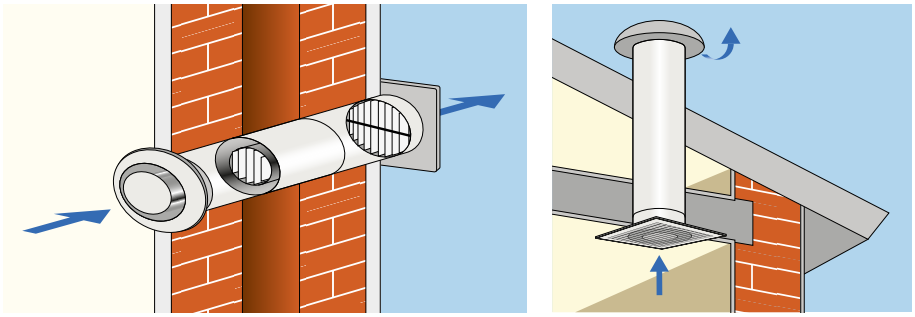


Figure 8.2 Examples of mechanical ventilation

UV lamps

Product lifetime: 7–14 months; to be wiped every month with 70° alcohol.

Figure 8.3 UV lamp

8.3 Individual respiratory protection

- Surgical face masks prevent the passage of the wearer's germs to others but do not protect the wearer from the germs of others.
- N95 respirators are the last line of defence 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.

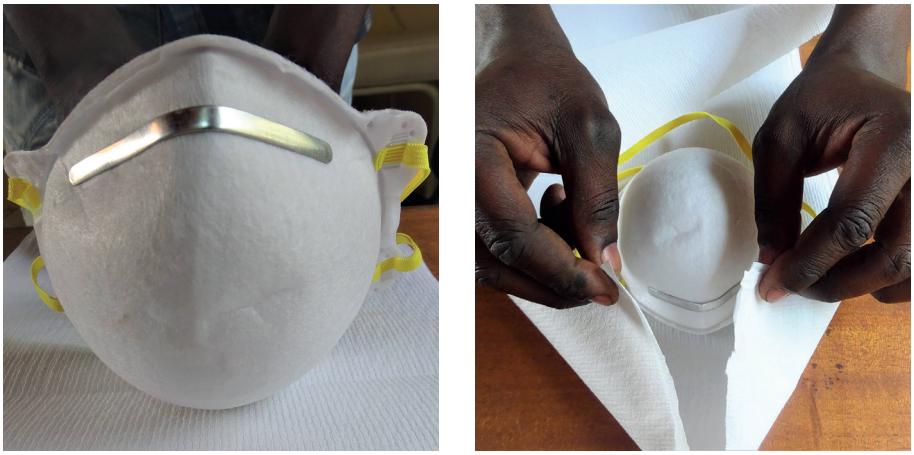


Figure 8.4 N95 Respirator (left) and its daily protection from dust (right)

Annexes

Annex 1

What to do when laboratory resistance test results are anomalous or discordant

Any resistance result (on any type of testing) in a person with risk factors for resistance should be initially considered as resistant.

1) **Cases unlikely to be R-resistant which are RR on Xpert** (e.g. new cases in settings with low RR prevalence). Possible identification or clerical error.

   a. Interpretation: repeat Xpert test with another sample and take the second result as correct.

2) **RS on Xpert, although R resistance very likely** (e.g., treatment failures, relapses after retreatment, contacts of RR-TB patients).

   a. Interpretation: Xpert may not detect resistance due to a few types of mutations. If possible, refer for phenotypic LJ-DST.

3) **MTB detected and RR on Xpert but culture-negative**

   a. Causes: insufficient sample amount, delays in sample transportation, poor viability of the bacilli, incorrect laboratory procedures (decontamination, quality of culture medium, incubation, identification errors, etc.). Dead bacilli yield a positive Xpert result.

   b. Interpretation: retain Xpert result (RR); but disregard if it concerns a cured RR case.

4) **MTB detected and RS on Xpert but RR on LPA**

   a. Causes: laboratory errors; hetero-resistance (coexisting susceptible and resistant bacterial populations). Depending on the viability of the bacteria, DST may yield different resistance profiles on different samples. Hetero-resistance is much better detected using LPA than by Xpert, and is clinically significant. Beware of possible technical errors in case of LPA: poorly developed wild-type bands that are inaccurately interpreted as indicative of resistance.

   b. Interpretation: retain LPA result (RR).

5) MTB detected and RR on Xpert but RS on LPA

a. Causes: mutations are more likely to be undetected by LPA at either end of the amplified segment; hetero-resistance detected accidentally by either test. Possible LPA reading error: wild-type band too weakly developed but not interpreted as indicative of resistance.

b. Interpretation: retain Xpert (RR) result.

6) MTB detected and RR on Xpert, but RS on culture with DST

a. Causes: silent mutations that do not modify the target protein. Common only in countries with very low prevalence of RR, but very rare in countries with high prevalence of RR. DST for R in culture could yield false susceptible results due to low resistance or due to poor growth of resistant bacilli (quite frequent, especially in liquid culture), partly associated with poor technique.

b. Interpretation: retain Xpert (RR) result.

7) MTB detected and RS on Xpert, but RR on culture with DST

a. Causes: rare mutations outside the rpoB gene region not covered by the commercial test. Heteroresistance undetected on Xpert.

b. Interpretation: retain culture result with DST (RR).

Annex 2

Preparation, transport and processing of sputum samples

(Based on unpublished data of the Institute of Tropical Medicine, Antwerp, Belgium)

a) For tests with dead bacilli (molecular tests)

Principle

When preparing a sample from a patient with presumptive RR-TB, the health worker should preserve the smear-positive sample in ethanol for dispatch to a laboratory equipped with Xpert or LPA (GenoType® MTBDRPlus or MTBDRsl) equipment.

In order to ensure inactivation of the TB bacilli, the final concentration of ethanol should be approximately 70%. This can be attained by adding 1 volume of sputum to 2 volumes of commonly available, industrial-quality ethanol at about 95%.

Equipment

Option 1:

A 50 ml conical tube with hermetically closing screwcap (Falcon®-type) containing 10 ml of 95% ethanol.

Or

Option 2:

- 50 ml tube (Falcon®-type)
- 95% ethanol (denatured alcohol)

Preparation

- Leave sputum in pot on the bench overnight to allow it to liquefy;
- The following day, shake the sample slowly and gently in circular movements for several seconds with the cap closed;
- Let stand for 15–30 min before opening;
- Assess the volume of the sample.

Option 1:

If the volume of the sputum sample is <5 ml, reduce the volume of ethanol in the 50 ml Falcon® tube until the quantity of ethanol is approximately two times that of the sputum. If sample volume is >5 ml, add ethanol from another 50 ml tube to ensure that the volume of the ethanol is approximately double that of sputum volume.

Option 2:

- Pour two volumes of 95% ethanol for each volume of sputum into a 50 ml tube, pour the sample into the 50 ml tube containing the 95% ethanol, allowing it to flow down the sides of the tube;
- Hermetically seal the 50 ml tube and shake the test tube by inverting it about 20 times;
- Write the name of the patient and that of the BMU on the test tube with an indelible marker pen;
- Keep the test tube at room temperature until the following day to ensure that the bacilli are dead;
- Fill out the Xpert Test Request Form.

Transport

No security packaging is necessary to transport the test tubes, as the bacilli are dead. Ensure that the tubes are properly closed and place them in a thick, flame-sealed plastic bag for transportation.

If air transport is used, the total volume of ethanol should not exceed 30 ml per tube or 300 ml per package of x number of test tubes (Inflammable, Dangerous Goods Class A according to International Air Transport Association regulations).

Laboratory procedures for Xpert testing:

- Transfer a minimum of 2 ml of the sputum-ethanol mixture into the cartridge without using the Cepheid reagent.

Laboratory procedures for LPA:

- Centrifuge the test tube at 3,000g for 15 min;
- Remove the supernatant;
- Put the sediment back into suspension in 50 ml of sterile distilled water;
- Carry out a second centrifugation at 3,000g for 15 min;
- Remove the supernatant and use the sediment.

b) For culture on solid egg-based medium

Principle

This form of transportation uses antiseptic CPC, which enables live TB bacilli to be conserved at room temperature for a month.

Materials required

- 50 ml (Falcon®) tubes that are sterile, conical, plastic, graduated (do not re-use tubes).
- 1% CPC solution: dissolve 20 g of salt (NaCl) and 10 g of CPC powder in 1,000 ml of distilled water and place the mixture in an autoclave; keep the mixture at room temperature to avoid precipitation and inactivation (the lifespan of the solution is 1–2 years); fill each 50 ml tube aseptically with 5 ml of the solution.
- Sanitary paper, cotton, labels, adhesive/duct tape, plastic bags, plasticised envelopes, cardboard cartons.

Preparation

- Discontinue all anti-tuberculosis drugs for 1–2 days.
- Provide the patient with two 50 ml Falcon® tubes containing 5 ml of CPC solution (see below for details) and ask him to collect a sputum sample in the morning.
- Ensure that the tubes are hermetically sealed without using excessive force to avoid cracking the cap.
- Shake slowly and gently to mix the sputum with the CPC solution.

- Label the tube and give a unique number to each label (leukoplast-type adhesive label or coated paper covered by transparent adhesive tapes); do not write on the tube with an indelible marker pen as writings may come off with the chemicals used in the laboratory.
- Record data in a register with the sample identification number and details about the patient; to create an ID number for each sample, the code of the town (e.g., RAB), the year (e.g., 17) and the sequential number of the laboratory register (e.g., 001) could be used, with the extension "A" or "B" to indicate samples from the same patient collected on 2 successive days. These numbers should never be used again; if other samples are later collected from the same patient, they should have different ID numbers.
- Always preserve the tubes with the CPC solution, regardless of whether with or without sputum, at room temperature (CPC crystallises at low temperatures).

Packaging

- Wrap each tube separately in absorbent paper (tissue paper).
- Completely wrap the tubes in cotton.
- Place the tubes in a strong plastic envelope and hermetically flame-seal it; Ziploc bags may also be used.
- Place the envelope in a strong cardboard box and add absorbent material.
- Attach a list of samples (each with a unique ID number and the full name of the patient) to the package after having first placed the samples in a plastic bag.
- Hermetically seal the box with adhesive tape and stick the address label on the box.

Transport

- Samples should ideally be delivered within a maximum period of 10 days after collection; avoid exceeding 4 weeks since then few or no viable acid-fast bacilli (AFB) will remain.
- The most rapid means of transport should be used to send the tubes.

c) For culture in liquid medium or agar

CPC or other detergent-type antiseptic substances are not suitable for transporting sputum if culture is performed in liquid medium (7H9 medium, as in the case of automated MGIT™) or on agar-based solid medium (Middlebrook media). The product remains active and bacilli growth is inhibited. It should be noted that Ziehl-Neelsen and auramine staining of sputum transported in CPC often yields false-negative results. Smear microscopy of such samples on arrival at the reference laboratory is of little or no use and should never be used for diagnosis if a site laboratory result obtained directly from sputum is available.

Samples intended for liquid or agar culture should be transported and processed rapidly and refrigerated (cold chain). Optimal results are only possible with samples that are processed immediately after collection in the laboratory. The longer the period required for transportation and the lower the number of bacilli at the beginning, the poorer the results are likely to be – either due to the excessively high rate of soft decontamination (for example, when the standard 1% NaCl-NaOH is used) or due to the large number of false-negatives in case of hard decontamination (for example, when Petroff's method is used for a long time). A double dose of the PANTA™ antibiotic mix (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, azlocillin; BD, Sparks, MD, USA) or Selectatabs™ (Mitchison's method) if added to the medium may help reduce contamination without excessively affecting the decontamination technique.

Annex 3

Laboratory test results and drug safety management

	AST (IU/l)	*ALT (IU/l)*	*Creatinine (µmol/l)*	*K^+ (mEq/l)*	*Lactate (mmol/l) Venous blood*
Normal values	*X–N*	*X–N*	*X–N*	*≥3.5*	*0.5–2*
Grade 1	1.25–2.5 x N	1.25–2.5 x N	>1–1.5 x N	3.2–3.4	1.9–2.9
Grade 2	>2.5–5 x N	>2.5–5 x N	>1.5–3 x N	2.8–3.1	3–3.9
Grade 3	>5–10 x N	>5–10 x N	>3–6 x N	2.5–2.7	4–4.9
Grade 4	>10 x N	>10 x N	>6 x N	<2.5	≥5

Note: X = lower normal value according to national guidelines; N = upper normal value according to national guidelines

	Lipase° (IU/l)	*Hb (g/dl)*	*Platelets (/mm3)*	*Neutrophils (/mm3)*
Normal values	*X–N*	*>10.5*	*>100,000*	*>1,500*
Grade 1	>1–1.5 x N	9.5–10.5	75,000–99,999	1,000–1,500
Grade 2	>1.5–2 x N	8–9.4	50,000–74,999	750–999
Grade 3	>2–5 x N	6.5–7.9	20,000–49,999	500–749
Grade 4	>5 x N	<6.5	<20,000	<500

Note: X = lower normal value according to national guidelines; N = upper normal value according to national guidelines

° Ref. Compassionate use program of bedaquiline. Janssen 2012.

	QTc	*Hearing loss*	*Vomiting*	*Diarrhoea*	*Peripheral neuropathy*
Normal values	*Men ≤450 ms Women ≤470 ms*	*0–20 dB*			
Grade 1		Mild: 21–40 dB	Transient: 2–3 episodes/day or duration ≤1 week	Transient: 3–4 stools/day or duration ≤1 week	Discreet pain; no treatment
Grade 2	Men 450–500 ms Women 470–500 ms	Moderate: 41–70 dB	Repeated 4–5 episodes/day or duration >1 week	Persistent: 5–7 stools/day or duration >1 week	Permanent moderate pain; vitamin B6
Grade 3	>500 ms	Severe: 71–90 dB	Vomiting for 24 h; orthostatic hypotension	>7 stools/day or necessitating a drip; blood in stools	Permanent severe pain; NSAIDs, antidepressants
Grade 4	>500 ms with symptoms	Profound: >90 dB	Hypovolemic shock	Hypovolemic shock	Pain unbearable despite treatment

	Arthralgia	*Myalgia*	*Hypothyroidism*	*Skin rashes*	*Mental disorders*	*Optic neuritis*
Grade 1	Arthralgia	Slight, without limitation of activity	Subclinical hypothyroidism TSH <12 mU/l; Normal free T4 levels	Erythema; moderate pruritus	Minor anxiety	
Grade 2	Arthralgia with moderate limitation to functions	Muscular weakness; limitation of activity	Hypothyroidism without complications; treatment necessary	Extensive maculo-papular rash, with or without pruritus	Anxiety requiring treatment or minor depression	
Grade 3	Arthralgia with significant limitation to functions	Severe weakness with signifi-cant limitation to daily activities	Severe hypothyroidism with clinical signs; urgent treatment, hospitalisation	Papular-vesicular or oozing rash, purpura, skin or mucous ulcers	Major depression requiring treatment	Sudden loss of vision, retro-ocular pain, dimin-ished photo motor reflex
Grade 4		Myonecrosis	Myxoedema coma	Bullous lesions (Lyell or Stevens Johnson syn-drome), febrile erythroderma, skin necrosis	Acute psychosis (suicidal ideas, manic state, hallucinatory delirium)	Blindness

Ref.: Adapted from ANRS* scale for the gradation of the severity of adverse events among adults (2008).

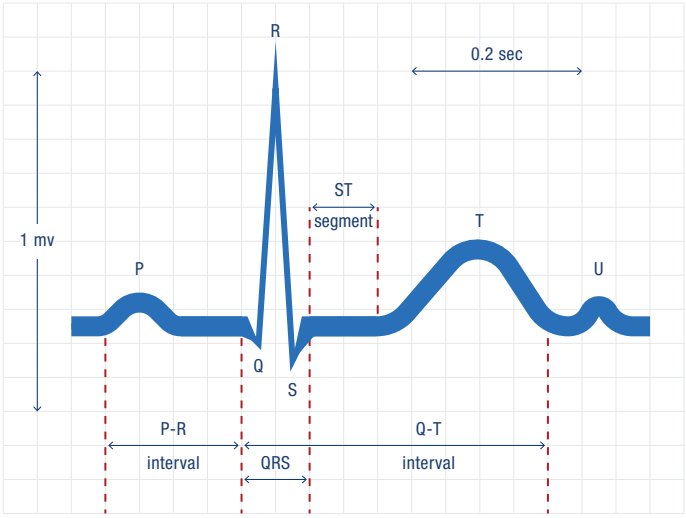
*Agence Nationale pour la Recherche sur le SIDA et les hépatites (National AIDS and Hepatitis Research Agency), Paris, France

Annex 4

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 depolarise and repolarise.
- 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, ischaemia etc.).
- Hypothyroidism.
- **Hypokalaemia**, 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.

What is the importance of the QTc?

A prolongation of the QTc signifies that the heart muscle takes longer than normal to repolarise 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.

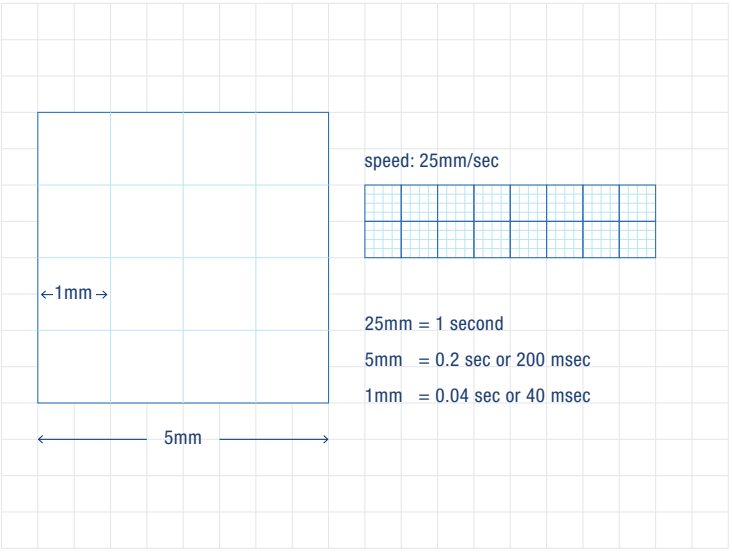
Measurement of the QTc

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.

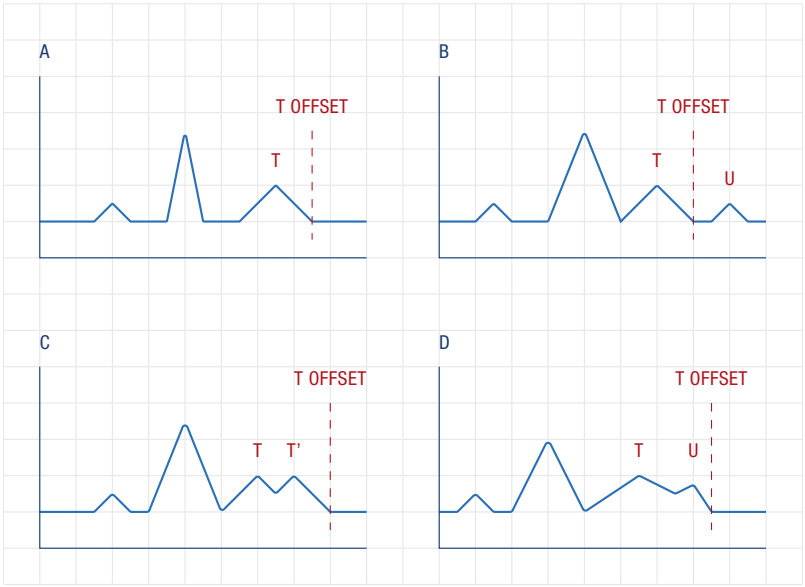
Step 1: measuring the QT interval

- 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.
- Hypokalaemia 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.

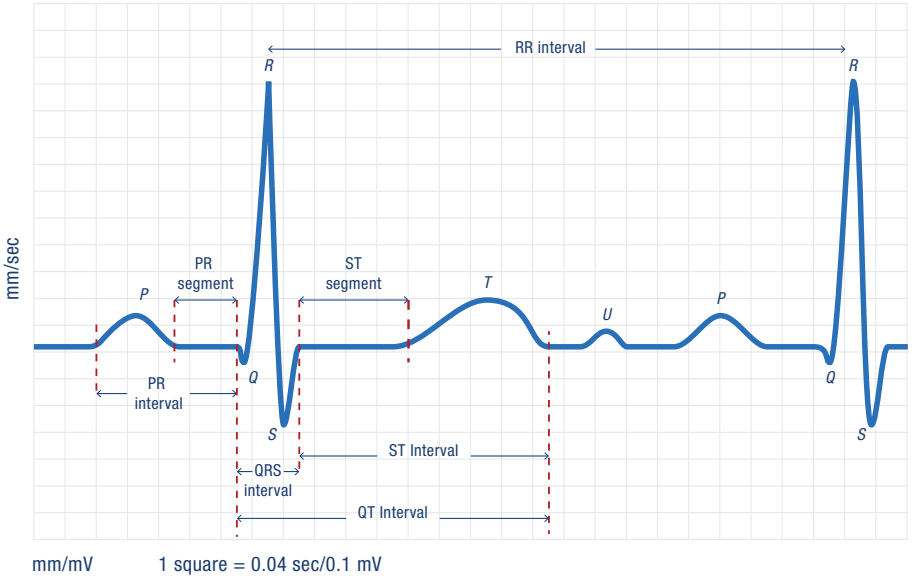
B) Small U wave distinct from the T wave: measure the QT interval at the end of the T wave.

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 depolarisation 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 Framingham formula is reliable and used to calculate QT interval correction.

$$QT_{cFra}(s) = QT + 0.154\ [1\text{-}RR(s)]$$

- QT interval: distance between the start of the QRS complex and the end of the T wave in seconds (number of small squares x 0.04).
- R-R: distance between two R waves: R et R' in seconds (number of small squares x 0.04).
- $QT_{cFra}(s)$ x 1,000 = $QT_{cFra}(ms)$.

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

$$QT_{cF}(s) = QT/\sqrt[3]{RR}$$

Annex 5

Audiometry: description, measurement and clinical implications

Monitoring of hearing loss is important for two reasons:

- With early detection, it is possible to reduce the dose or discontinue use of the drug responsible, thus preventing further hearing loss.
- If hearing loss is significant, hearing aids should be provided for the patients.

There are three types of hearing loss:

- Conductive hearing loss: damage to the external ear (usually a blocked canal, for example, earwax blockage), or damage to the middle ear (otitis, ossicle damage, etc.).
- Neurosensorial hearing loss: dysfunction of the internal ear (cochlea), which generally results in damage to hair cells or the auditory nerve. **In MDR-TB treatment, the use of second-line injectable drugs can cause this type of hearing loss**.
- Mixed hearing loss: a combination of conductive hearing loss and neurosensorial loss.

The first step in the detection of auditory disorders is to eliminate the possibility of conductive hearing loss by examining the ear canal with an otoscope.

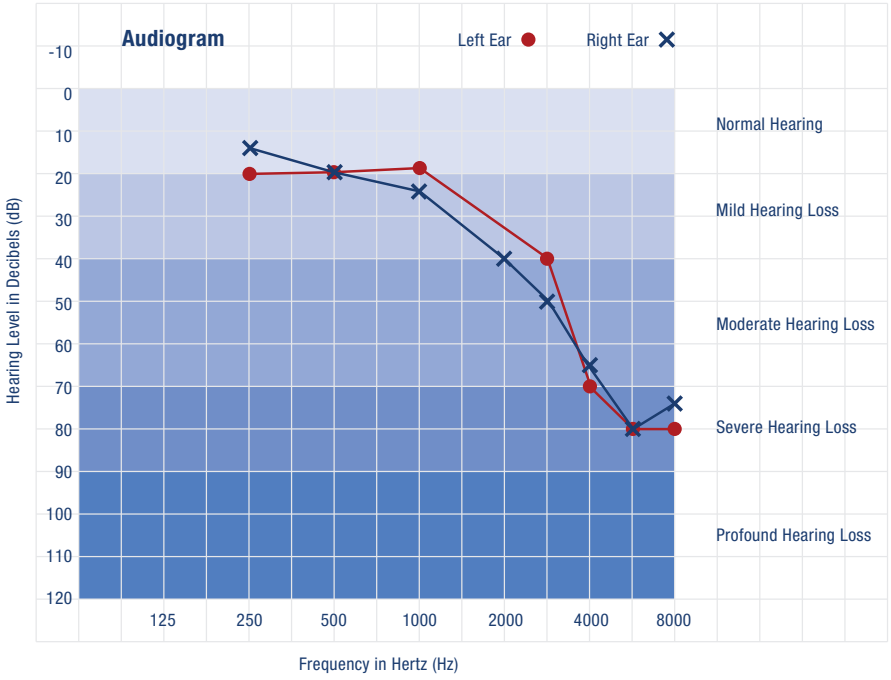
The second step consists of carrying out an audiometry.

Audiometry:

- This test involves playing a pure frequency sound (measured in Hertz, Hz) at an intensity (measured in decibels, dB) with increasing loudness to determine at which intensity the patient is able to hear.
- An audiometry is carried out by using an electronic device called an audiometer.

Desirable characteristics and features of the audiometer:

- Frequencies between 125 and 8,000 Hz.
- Powered by (A/C) mains electricity and by batteries.
- Clear tone of sounds to avoid the need for a soundproof booth. An ordinary silent room should suffice.
- Easy for both the patient and the health care worker to use, so training can be kept to a minimum.



- An audiogram is a graph on which the audiometry results are plotted.
- It shows the lowest sound that an individual can hear at specific frequencies from the lowest to the highest.

Measurement of hearing loss

- Average hearing loss (AHL) is calculated for each ear at frequencies of 500, 1,000, 2,000 and 4,000 Hz.

$$AHL = \frac{HL500Hz+HL1,000HZ+HL2,000Hz+HL4,000Hz}{4}$$

- Round up the AHL to the upper bound.
- Consider the worst hearing ear to grade the loss.
- Determine the degree of AHL according to the rating scale for AEs.

Grade 1:Mild	*Grade 2:Moderate*	*Grade 3: Severe*	*Grade 4: Profound*
Mild deficit: 21–40 dB	Moderate deficit: 40–70 dB 1st degree: 41–55 dB 2nd degree: 56–70 dB	Severe deficit: 70–90 dB 1st degree: 71–80 dB 2nd degree: 81–90 dB	Profound deficit: >90 dB 1st degree: 91–100 dB 2nd degree: 101–110 dB 3rd degree: 111–120 dB
Speech perceived if the voice is normal. Difficulty in perceiving low-intensity sounds and soft voices.	Difficulty in perceiving even loud sounds and loud voices. Provide hearing aids.	Words only heard when shouted in the ear. Provide hearing aids.	Words cannot be understood at all. Only very loud noises are heard.

Practical example:

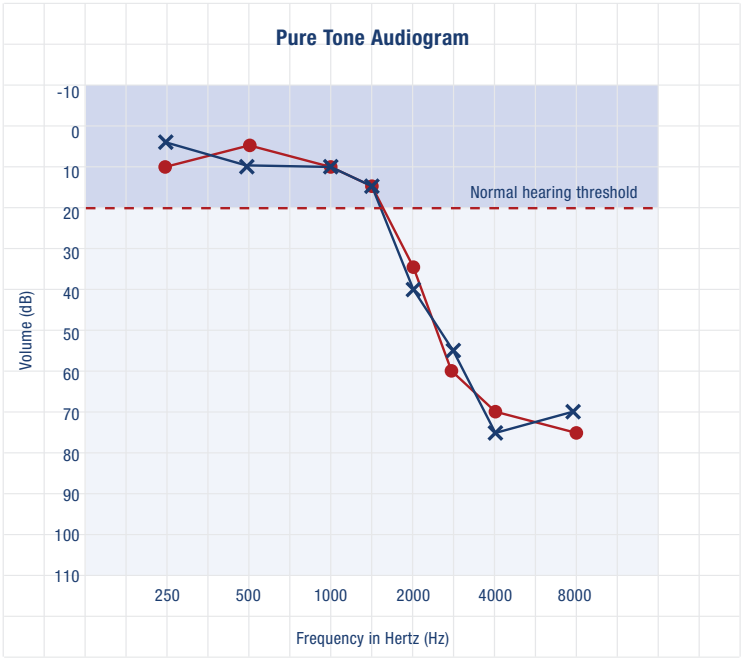
Hearing loss

Frequency (Hz)	*Right ear (dB)*	*Left ear (dB)*
500	30	55
1,000	50	65
2,000	65	70
4,000	65	75
Average hearing loss	53*	67°

*52.5 dB rounded to 53

°66.25 dB rounded to 67

- AHL in the ear with poorer hearing: 67 dB (left ear)
- Degree of loss: D2 (second band).



Sample audiogram

Annex 6

Forms

6.1 REQUEST FORM FOR SPUTUM SMEAR MICROSCOPY

NATIONAL TUBERCULOSIS CONTROL PROGRAMME MINISTRY OF PUBLIC HEALTH

Unit referring patient: _____

Date of collection: _____

Full name of patient: _____

Age:_____ Sex: ☐ M ☐ F

Address *(village and district)*: _____

Reason for testing: ☐ Diagnosis ☐ Monitoring If monitoring, which month: _____

If monitoring:

TB BMU no. of patient: _____

MDR-TB Unit no. of patient: _____

Full name of the health worker requesting the test *(printed name in full)*: _____

Signature of the health worker requesting the test: _____

RESULTS (to be completed in the laboratory)

Serial number of laboratory test: _____ Date of receipt: _____

☐ Ziehl-Neelsen ☐ Auramine

Collection date	Sample	Visual appearance*	Result				
			Negative	Scanty N. AFB	+	++	+++
	1						
	2						

*Muco-purulent, traces of blood, saliva

Examination carried out by *(printed name in full)*: _____

Date: _____/_____/_____ Signature: _____

This form should be duly completed and sent to the Treatment Unit.

6.2 REQUEST FORM FOR XPERT TEST

NATIONAL TUBERCULOSIS CONTROL PROGRAMME MINISTRY OF PUBLIC HEALTH

BMU: _____ Region: _____ District: _____

Date: _____/_____/_____

Full name of patient: _____

Age: _____ Sex: ☐ M ☐ F Telephone: _____

Address: _____

Date and result of microscopy: ____/_____/____ _____

Laboratory no: _____ TB registration no.*:_____ *(*to fill in if registered TB patient)*

Nature of the sample: ☐ Sputum ☐ Other Specify: _____

HIV: ☐ Negative ☐ Positive ☐ Unknown

Reason for testing *(tick one of the following boxes)*:

☐ Suspected rifampicin resistance in a smear-positive pulmonary TB patient with previous treatment history

☐ Failure of retreatment ☐ Failure of first-line treatment

☐ Relapse after retreatment ☐ Relapse after first-line treatment

☐ Return to treatment after lost to follow-up

☐ Contact of known RR-TB patient

☐ Diagnosis of TB *(smear-negative, but clinical suspicion)*

Details and particulars of the prescriber *(necessary for rapid return of result)*

Printed Name in Full: _____Telephone: _____

Signature: _____

Xpert results

Date	Xpert no	Results	
		MTB*	RIF**

If error: provide error code: _____

** D (Detected), ND (Not detected), E (Error), Iv (Invalid) ** S (Susceptible), R (Resistant), Id (Indeterminate)*

Test performed by *(printed name in full)*: Name: _____ Designation: _____

Signature: _____

6.3 REQUEST FORM CULTURE/DST/LPA

NATIONAL TUBERCULOSIS CONTROL PROGRAMME MINISTRY OF PUBLIC HEALTH

☐ **Request for culture** ☐ **DST** ☐ **First-line LPA** ☐ **Second-line LPA**

Full name of patient: _____ Patient's BMU: _____

Age: _____ Sex: ☐ M ☐ F Telephone: _____

Address: _____

Reason for testing

☐ Initial test before RR-TB treatment initiation

☐ Follow-up during RR-TB treatment; if yes, which month: _____ ☐ Other, specify: _____

MDR-TB Reg. Number: _____

Name of the laboratory performing the Xpert test showing resistance to rifampicin: _____

Sample type: ☐ Sputum ☐ Other, specify: _____

Method of sample transportation: ☐ fresh sputum ☐ in CPC ☐ in alcohol

Full name in print of the agent requesting the test: _____

Signature: _____ Telephone: _____

Culture result Date: ____/_____/____

N°	Contaminated	Negative	Non-tuberculous mycobacteria (type)	*Mycobacterium tuberculosis* complex			
				1–9 colonies (#)	10–100 (1+)	> 100–200 (2+)	>200 (3+)

DST result Date: ____/_____/____

ID#	S = Susceptible ; R = Resistant ; C = Contaminated ; ND = Not done								
	H			R	E	S	Mfx or Gfx		Am
µg/ml	☐ 0.2	☐ 1	☐ 5	☐ 40	☐ 2	☐ 4	☐ 0.5	☐ 2	☐ 30
Result									

Note: *Concentrations showed apply to LJ. To be adapted according to the method used.*

LPA result Date: ____/_____/____

ID#	R	H	FQ	Km	Am	Cm
Result:						
Mutation:						

S: *susceptible;* ***R:*** *resistant;* ***LR:*** *low resistance;* ***HR:*** *high resistance;* ***Mutation:*** *specify the mutation*

Test performed by: _____ Signature: _____

(printed name in full)

VARIABLES FOR LABORATORY REGISTERS 6.4A AND 6.4B (SEE BELOW)

Name of laboratory/town	
Laboratory ID	Name of laboratory
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

Sex	
F	Female
M	Male

Origin
Enter name of BMU which referred the patient and the region of origin

Type	
F1	Failure of first treatment
F2	Failure of retreatment
R1	Relapse of first treatment
R2	Relapse of retreatment
RT	Retreatment after default
RRC	RR-TB contact
PTB Sm–	Diagnosis of tuberculosis (smear-negative, but clinical suspicion)
O	Other

HIV status	
Neg	Negative
Pos	Positive

MTB	
D	Detected
ND	Not detected
E	Error
Iv	Invalid

Resistance to rifampicin	
S	Susceptible
R	Resistant
Id	Indeterminate

Status of patient	
T	Treated
NT	Not treated

Management unit	
1	
2	
3	
4	

Reasons for non treatment	
MI	Underage minor
XR	XDR-TB case
AT	Already treated using second-line drugs
PW	Pregnant woman
CI	Other medical contraindications
RC	Refusal to consent/treatment
SE	Patient searched for
ND	No drugs
NR	Non resident
SP	Social problems
DI	Died
O	Other

6.4A LABORATORY REGISTER FOR PATIENTS TESTED USING XPERT

NATIONAL TUBERCULOSIS CONTROL PROGRAMME | MINISTRY OF PUBLIC HEALTH

Name of laboratory: _____

No.	Full name	Date of testing	Laboratory no.	Smear microscopy		Age in years	Sex F/M	Origin Region/ BMU	Type F1, F2, R1, R2, RT, RRC, PTB Sm–, O	HIV Neg, Pos	MTB D, ND, E, Iv	Rifampicin resistance R, S, Id
				Date	Result							
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												

6.4B LABORATORY REGISTER OF PATIENTS WITH CONFIRMED RR-TB WITH TREATMENT DETAILS

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Name of laboratory: _____

No.	Full name	Date of testing	Laboratory no.	Smear microscopy		Age in years	Sex F/M	Origin Region/ BMU	Type F1, F2, R1, R2, RT, RRC, PTB Sm–, 0	Rifampicin resistance R	Status			
				Date	Result						(T/NT)	Reasons for no treatment	Date of treatment initiation	MDR-TB Unit
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														

6.5 RR/MDR-TB TREATMENT CARD (1/7)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Name of RR/MDR-TB Unit: _____

RR/MDR-TB Registration number: _____

Full Name: _____

Start date of RR/MDR-TB treatment: _____

Last TB file registration number/year: _____ BMU: _____

Pulmonary form or extra-pulmonary TB: ☐ PTB and/or ☐ EPTB

Address and tel no.: _____

If EPTB, site: _____

Name, address and tel no. of a guarantor: _____

Height: _____

_____

_____

_____

Age: _____ Sex: ☐ M ☐ F

MDR-TB at the start of treatment confirmed or suspected: ☐ C ☐ S

Has already taken second-line drugs for more than a month: ☐ Yes ☐ No

If yes, which one(s): _____

Previous treatment episodes

Start date (year, if known)	**Regimen**	**Result**

Zones affected

	Left lung	**Right lung**
0		
1		
2		
3		

Serology

	Date	**Result**
Test** (P,N,I, R,A)		
CD4		
CPT		
ARV details page 3/7		

**P = Positive, N = Negative, I = Indeterminate, R = Refusal, A = Not done
CPT = cotrimoxazole preventive treatment

Type of patient

☐ New (N)
☐ Relapse Cat1 (R1)
☐ Relapse retreatment (R2)
☐ Failure Cat1 (F1)
☐ Failure retreatment (F2)
☐ Return to treatment (RT)
☐ Other (O)

6.5 RR/MDR-TB TREATMENT CARD (2/7)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Treatment monitoring

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M15	M21
Date														
Smear§														
Culture§														
HIV§														
Audiogram§														
Weight (kg)§														
CBC @														
Creatinine§														
K+§														
ALT§														
AST§														
Glucose														
ECG (M0: Day 1 and Day 7)§														
Pregnancy test§														
Chest X-ray @														

§ insert result @ put a cross if done

Dose of modified drug

If yes, which one: _____ Date: _____/_____/_____ Reason: _____

If yes, which one: _____ Date: _____/_____/_____ Reason: _____

6.5 RR/MDR-TB TREATMENT CARD (3/7)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Month of treatment	Smear		
	Date*	No.	Result
Before**			
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
After treatment			
15			
21			
27			
33			

Month of treatment	Culture		
	Date*	No.	Result
Before**			
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
After treatment			
15			
21			
27			
33			

*Date of sputum collection. **Date when the sputum which served to identify the case as MDR-TB was collected

Smear results

Not done/absent	A
No AFB	Neg (N)
1–9 AFB/100 fields	Scanty (S)
10–99 AFB/100 fields	+
1–10 AFB/field	+ +
> 10 AFB per field	+ + +

Culture results

Not done/absent	A
No colony	Neg (N)
Contaminated	Contamin. (C)
<10 colonies	Scanty (S)
10–100 colonies	+
101–200 colonies	+ +
>200 colonies	+ + +

If on antiretroviral treatment, list the drugs taken

6.5 RR/MDR-TB TREATMENT CARD (4/7)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME MINISTRY OF PUBLIC HEALTH

DST result (R = Resistant; S = Susceptible; C = Contaminated; N = Not tested)

Sputum collection date	Method of analysis	Test result date	R	H	S	E	Am	Fq	Others

Treatment regimen (number of tablets or in mg for amikacin)

Date	Am	Mfx or Gfx	Pto	H	Cfz	E	Z	Other (s)

Drugs stopped definitively: ☐ Yes ☐ No

If yes, which one: _____ Date: _____/_____/_____ Reason: _____

If yes, which one: _____ Date: _____/_____/_____ Reason: _____

6.5 RR/MDR-TB TREATMENT CARD (5/7)

Table of adverse events

Describe adverse events for each month. If there are no adverse events, specify “No adverse events”

Month of treatment	Date of appearance	Adverse events and steps taken
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		

6.5 RR/MDR-TB TREATMENT CARD (6/7)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Clinical monitoring and follow-up. Describe steps taken each month

Month 0 date: _____

Month 1 date: _____

Month 2 date: _____

Month 3 date: _____

Month 4 date: _____

Month 5 date: _____

Month 6 date: _____

Month 7 date: _____

Month 8 date: _____

Month 9 date: _____

Other months: _____

6.5 RR/MDR-TB TREATMENT CARD (7/7)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Name of RR/MDR-TB Unit: _____

RR/MDR-TB Registration number: _____

Name of patient: _____

Start date of RR/MDR-TB treatment: _____

Drugs to administer daily under DOT:

Amikacin	Isoniazid 300	Prothionamide 250	Moxifloxacine 400 or Gatifloxacine 400	Clofazimine 100	Ethambutol 400	Pyrazinamide 400

Intensive phase*

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Continuation phase*

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

*Mark with X the days of supervised drug administration. When the patient takes no drugs, mark with 0

Date of treatment completion: _____ /_____ /_____ ☐ Cured ☐ Treatment completed ☐ Failure ☐ Died ☐ Lost to follow-up ☐ Transferred out

6.6 RR-TB TREATMENT REGISTER (1/2)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

RR-TB register no.	Start date of MDR-TB treatment	Full name of patient	Sex M/F	Age	Address (Town)	BMU/TB register no./year	Type of TB (PTB/ EPTB)	Type of patient (N, R1, R2, F1, F2, RT, T, O)	Second-line drugs already received (Y/N)	HIV serology result (P, N, I, R, NF)	On ART	Molecular testing for rifampicin resistance (date/result)	Other susceptibility tests (date/method)	DST result R = resistant; HR = highly resistant; WR = weakly resistant; S = susceptible; C = contaminated; N = Not tested					Regimen (duration and composition)
														R	H	SLI	FQ	Other	
1																			
2																			
3																			
4																			
5																			
6																			
7																			
8																			
9																			
10																			

6.6 RR-TB TREATMENT REGISTER (2/2)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME

MINISTRY OF PUBLIC HEALTH

Smear (S) and culture (C) during treatment, treatment result and smear (S) and culture (C) results at months 6 and 12 after treatment

Month 0 Date Res		Month 2 Date Res		Month 4 Date Res		Month 6 Date Res		Month 9 Date Res		Month 10 Date Res		Month 11 Date Res		Month 12 Date Res		Month 14 Date Res		Month 16 Date Res		Month 18 Date Res		Month 20 Date Res		Treatment result		6 Months later		12 Months later		Observations
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	Date	Cured Completed Failure Died LTFU NE	S	C	S	C	

6.7 RR-TB DETECTION AND TREATMENT INITIATION REPORT

NATIONAL TUBERCULOSIS CONTROL PROGRAMME — MINISTRY OF PUBLIC HEALTH

RR-TB* Detection Report Form and initiation of second-line treatment

*RR-TB: rifampicin-resistant tuberculosis

Name of BMU: _____ Name of BMU employee in charge of report: _____

Patients registered during the _____ quarter of the year 20 _____ Date: _____ Signature: _____

1. Number of patients tested/screened positive for RR-TB during the quarter

(according to the date of the test results in the laboratory and/or BMU register)

Number of RR-TB tests performed on retreatment cases*	Number of RR-TB cases detected				Among RR-TB cases		
	Among retreatment cases*	Among RR-TB contacts	Among new cases	TOTAL	Number of FQ-resistant, pre-XDR-TB cases	Number of SLI-resistant pre-XDR-TB cases	Number of XDR-TB cases

2. Number of patients with RR-TB who began second-line treatment during the quarter

(according to treatment start date in the RR-TB register)

RR-TB cases	XDR or pre-XDR-TB cases	TOTAL

*Patients with suspected RR-TB = patients eligible for retreatment (relapse, failure, return to treatment)

1st quarter: 1 January–31 March **2nd quarter:** 1 April–30 June **3rd quarter:** 1 July–30 September **4th quarter:** 1 October–31 December

6.8 REPORT ON THE SECOND-LINE TREATMENT RESULTS

NATIONAL TUBERCULOSIS CONTROL PROGRAMME — MINISTRY OF PUBLIC HEALTH

Second-line treatment outcomes of RR-TB cases (from RR-TB register)

RR-TB: rifampicin-resistant TB, with or without resistance to other anti-tuberculosis drugs

Name of TB Centre: _____ Name of Centre employee in charge of the report: _____

Report completed at the end of _____ quarter of the year 20 _____ Date: _____ Signature: _____

Patients on short-course treatment	Cure[1]	Treatment completion[2]	Treatment failure[3]	Loss to follow-up[4]	Death[5]	Not assessed[6]	TOTAL
Patients who started treatment in the quarter that finished **12 months before**: In the_____ quarter of the year 20 ___							

Patients on long-course treatment	Cure[1a]	Treatment completion[2a]	Treatment failure[3a]	Loss to follow-up[4]	Death[5]	Not assessed[6]	TOTAL
Patients who started treatment in the quarter that ended **24 months before**: In the_____ quarter of the year 20 ___							

1 Cure: the patient has finished second-line treatment without sign of failure with at least 2 negative cultures at ≥30 days of interval after the end of the intensive phase.

1a Cure: the patient has finished second-line treatment without sign of failure with at least 3 negative cultures at ≥30 days of interval after the end of the intensive phase.

2 Treatment completed: the patient has finished second-line treatment without sign of failure but does not have 2 negative cultures at ≥30 days' interval after the end of the intensive phase.

2a Treatment completed: the patient has finished second-line treatment without sign of failure but does not have 3 negative cultures at ≥30 days' interval after the end of the intensive phase.

3 Treatment failure: 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, patient who after an initial conversion, has a reversion with two consecutive positive cultures, taken at least 30 days apart or, patient who has 2 consecutive positive smears with a degree of ≥2+ after ≥6 months and without improvement in clinical condition or, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs or, permanent discontinuation of treatment or of 2 or more drugs.

3a Treatment failure: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions.

4 Loss to follow-up: second-line treatment interrupted for ≥2 consecutive months.

5 Death: the patient died before completion of second-line treatment, regardless of cause.

6 Not evaluated: including transferred out cases whose treatment outcome is unknown.

6.9 SERIOUS ADVERSE EVENT FORM (1/2)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME MINISTRY OF PUBLIC HEALTH

Reporting Form for Serious Adverse Events due to RR, pre-XDR- and XDR-TB treatment

CONFIDENTIAL: To be sent to the Pharmacovigilance Department of the Ministry of Health and to NTP when a serious adverse event (SAE) is suspected

Is it a new adverse event? ☐ Yes ☐ No

If not, date of submission of the last SAE form: _____ /_____ /_____

1. Information about the patient

Surname: _____ First name: _____

Sex: ☐ male ☐ female Date of birth: _____ /_____ /_____

Pregnant woman: ☐ Yes ☐ No

TB card no.: _____ Telephone no.: _____

Address: _____

2. Suspected drug(s) and concomitant treatment

Name of the drug (commercial or generic)	Total daily dose	Date of first use of drug in question	Date when discontinued	Continues to be used

3. Information on serious adverse event (SAE)

Date of onset of SAE: _____ /_____ /_____ Date of end of SAE: _____ /_____ /_____

Description of SAE: _____

_____

_____

Reasons why the adverse event is serious:

☐ Death ☐ Life-threatening (specify): _____

☐ Hospitalisation or prolongation of hospitalisation

☐ Persistence of handicap or severity of the handicap (specify): _____

☐ Congenital abnormality

☐ Other (specify): _____

6.9 SERIOUS ADVERSE EVENT FORM (2/2)

4. Steps taken

☐ Discontinuation of drug
☐ Increase in dosage
☐ Decrease in dosage
☐ Dosage unchanged
☐ Unknown

5. Result of the SAE

☐ Cured/resolved
☐ Cure/resolution underway
☐ Resolution with sequelae
☐ Not cured/not resolved
☐ Died
☐ Unknown

6. Author of the report

Name: _____

Designation: _____

Name of MDR-TB Unit: _____

Address: _____

_____

_____

E-mail: _____

Signature: _____

ABOUT THE INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE (THE UNION)

The Union is a global scientific organisation with the mission to improve health among people living in poverty. We do that by conducting scientific research, working with governments and other agencies to translate research into better health for people around the world, and delivering projects directly in the field. The Union is made up of a global membership body of people who help to advance our mission, and a scientific institute that implements public health projects within countries. For close to 100 years, we have been leaders in the fight against some of the world's biggest killers, including tuberculosis, lung diseases and tobacco use.

ISBN: 979-10-91287-20-3