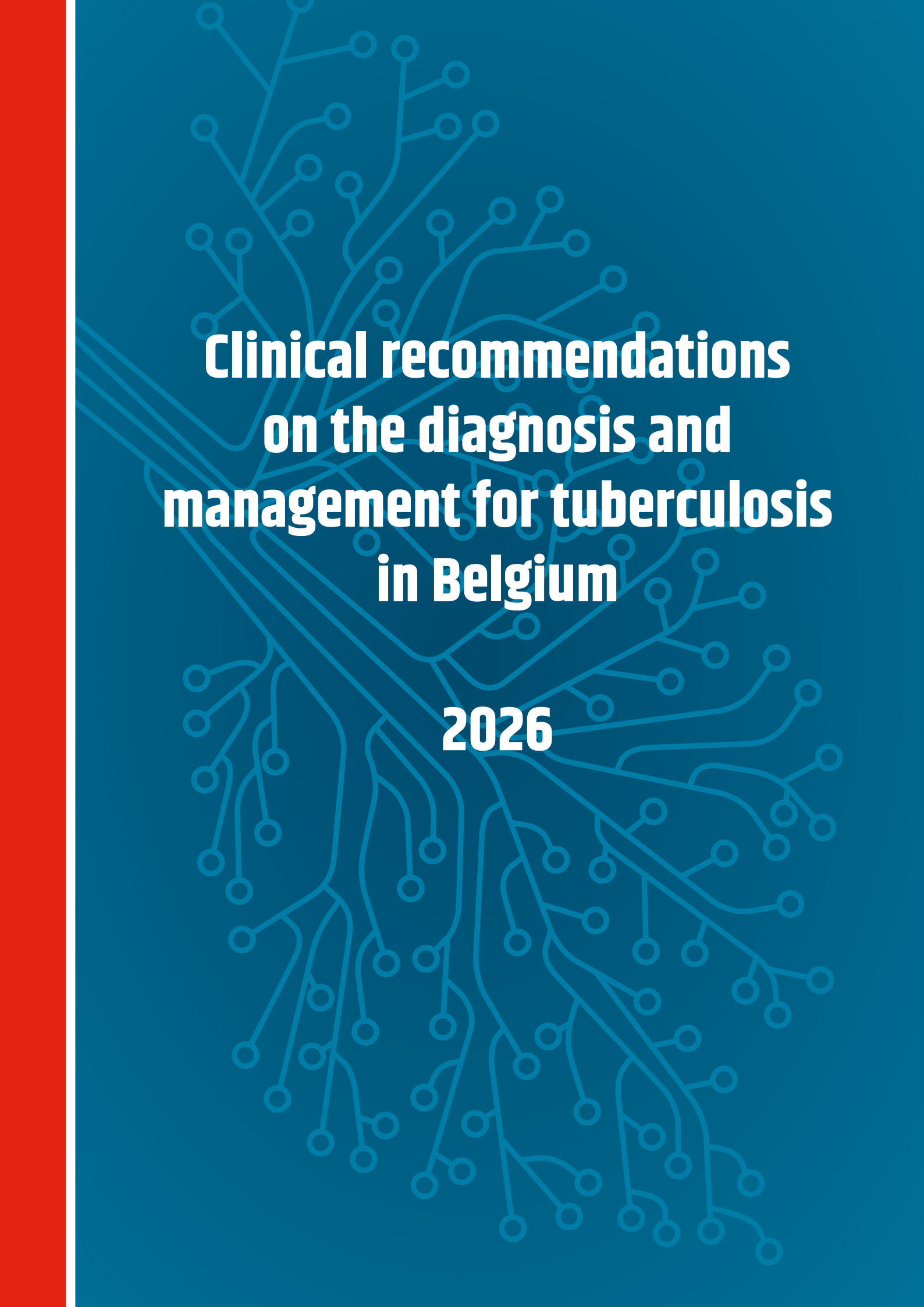




Clinical recommendations on the diagnosis and management for tuberculosis in Belgium

2026

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Abbreviations

ACE-I	Angiotensin-Converting Enzyme Inhibitor	d	day
AE	Adverse Event	DC	Dendritic Cells
AM	Alveolar Macrophages	DDIs	Drug-Drug Interactions
ART	Antiretroviral Therapy	dL	deciliter
ATP	Adenosine Triphosphate	DLM	Delamanid
AviQ	Agence pour une Vie de Qualité	DM	Diabetes Mellitus
BAL	Bronchoalveolar Lavage	DNA	Deoxyribonucleic Acid
BCG	Bacillus Calmette-Guérin	DOACs	Direct Oral Anticoagulants
BDQ	Bedaquiline	DOR	Doravirine
BELTA-TBnet	Belgian Tuberculosis Network	DOT	Directly Observed Therapy
BIC	Bictegravir	DR	Drug-resistant
bid	bis in die (two per day)	DS	Drug-susceptible
BPAL	Bedaquiline, Pretomanid and Linezolid	DST	Drug Susceptibility Testing
BPALM	Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin	DTG	Dolutegravir
CAB	Cabotegravir	EACS	European AIDS Clinical Society
CD	Cluster of Differentiation	EBUS	Endobronchial Ultrasound
cfr	confer (compare with)	ECG	Electrocardiogram
CFZ	Clofazimine	EFV	Efavirenz
CNS	Central Nervous System	e.g.	exempli gratia
COBI	Cobicistat	EMB	Ethambutol
CP	Continuation Phase	ENT	Ear, Nose and Throat
CPAS	Centre Public d'Action Sociale	EP-TB	Extra-Pulmonary Tuberculosis
CRP	C-Reactive Protein	ESAT6	Early Secreted Antigenic Target 6
CS	Cycloserine	ESR	Erythrocyte Sedimentation Rate
CSF	Cerebrospinal Fluid	Etc	et cetera (and other similar things)
CT	Computed Tomography	Eto	Ethionamide
CYP	Cytochrome P	ETR	Etravirine
		EU	European Union

EUS	Endoscopic Ultrasound	Kg	Kilogram
EVG/c	Elvitegravir/Cobicistat	L	Litre
FARES	Fonds des Affections Respiratoires	LDH	Lactate Dehydrogenase
FDG	Fluorodeoxyglucose	Lfx	Levofloxacin
FEDASIL	Agence fédérale pour l'accueil des demandeurs d'asile – Federal Agency for the Reception of Asylum Seekers	LN	Lymph Node
FFP2	Filtering Face Piece 2	LP	Lumbar Puncture
FQ	Fluoroquinolone	LPA	Line Probe Assay
FTC	Emtricitabine	LTBI	Latent Tuberculosis Infection
FTR	Fostemsavir	LZD	Linezolid
g	gram	M1 & M2	Macrophage Type 1 & 2
h	hour	MAO	Mono Amine Oxydase
HBV	Hepatitis B Virus	M. bovis	<i>Mycobacterium bovis</i>
HC	Hemocultures	MDR	Multi-Drug Resistant
HCV	Hepatitis C Virus	MDR/RR	Multi-Drug Resistant/Rifampicin Resistant
HEPA	High-Efficiency Particulate Air	Mfx	Moxifloxacin
HIV	Human Immunodeficiency Virus	mg	milligram
Hr-TB	Isoniazid-Resistant Tuberculosis	MGIT	Mycobacteria Growth Indicator Tube
HypoK	Hypokalaemia	mL	millilitre
HypoMg	Hypomagnesaemia	mm	millimetre
IBD	Inflammatory Bowel Disease	mmol	millimole
i.e.	id est (that is)	MPM	Meropenem
IFN-γ	Interferon Gamma	MRI	Magnetic Resonance Imaging
IGRA	Interferon Gamma Release Assay	MTBc	<i>Mycobacterium tuberculosis complex</i>
IL	Interleukin	MVC	Maraviroc
IM	Intramuscular	NaCl	Sodiumchloride
INAMI	Institut National d'Assurance Maladie-Invalidité	NADH	Nicotinamide adenine dinucleotide
INH	Isoniazid	NEMO	Nuclear Factor-κB Essential Modulator
INR	International Normalised Ratio	NK	Natural Killer
IP	Initial Phase	NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
IRIS	Immune Reconstitution Inflammatory Syndrome	NSAID	Nonsteroidal Anti-Inflammatory Drug
IU	International Units	NTM	Non-Tuberculous Mycobacteria
IV	Intravenous	NVP	Nevirapine

OCMW	Openbaar Centrum voor Maatschappelijk Welzijn	STAT	Signal Transducer and Activator of Transcription
Pa	Pretomanid	TA	Transaminases
PAS	Para-Aminosalicylic Acid	TAF	Tenofovir Alafenamide
PCR	Polymerase Chain Reaction	TB	Tuberculosis
PET	Positron Emission Tomography	TBI	Tuberculosis Infection
pH	potential of Hydrogen	TCA	Tricyclic Antidepressant
PI	Protease Inhibitor	TDM	Therapeutic Drug Monitoring
PICC	Peripherally Inserted Central Catheter	TDF	Tenofovir Disoproxil Fumarate
PLHIV	People Living with HIV	TGF-β	Transforming Growth Factor Beta
po	per os (by mouth)	tid	ter in die (3 times per day)
POCT	Point of Care Testing	TNF-α	Tumor Necrosis Factor Alpha
PPE	Personal protective equipment	TSH	Thyroid-Stimulating Hormone
PZA	Pyrazinamide	TST	Tuberculin Skin Test
QTc	Corrected QT Interval	ULN	Upper Limit of Normal
qd	quaque die (every day = once daily)	UMM	Unified Messaging Module
RAL	Raltegravir	US	Ultrasound
RCT	Randomised Controlled Trial	UVGI	Ultraviolet Germicidal Irradiation
RFB	Rifabutin	VRGT	Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering	WGS	Whole Genome Sequencing
RMP	Rifampicin	WHO	World Health Organization
RPV (LA)	Rilpivirine (Long-Acting)	XDR	Extensively Drug-Resistant
RR	Rifampicin Resistant	XR	X-Ray
RTV	Ritonavir	°C	Celcius
SLI	Second-Line Injectable	µg	microgram
SPN	Solitary Pulmonary Nodule		

1. Introduction

Controlling the TB epidemic is based primarily on early diagnosis and appropriate treatment of patients suffering from TB, as well as screening and treatment of the infection during its incubation or latency phase. The aim of this strategy is to cure, thereby limiting the transmission of the TB bacillus within the population.

In the current context, where TB is slowly declining in our country but where the development of resistance to first- and second-line anti-TB drugs has reached significant levels in several regions of the world, the aim of this document is to provide frontline healthcare staff with recommendations on how to detect and treat TB effectively.

The main principles for the diagnostic and therapeutic management of TB are set out in this document. They have been adapted to the emergence of new diagnostic tools and new anti-TB drugs, as well as to the epidemiological and healthcare context in Belgium, by a national committee of experts with experience in this field.

Belgian paediatricians specializing in TB are preparing detailed recommendations for children, which will be released soon. This document will expand on the current recommendations.

This practical manual is intended for all health care professionals involved in the management of TB.

Other aspects of TB control are discussed in publications available at www.fares.be and www.respiratoiregezondheid.be.

2. Epidemiology and Public Health considerations for TB prevention

2.1. General considerations

2.1.1. Epidemiology

TB is an infectious disease caused by *MTBc*. The bacillus spreads through the air and usually affects the lungs (pulmonary TB). Organs other than the lungs can also be affected, that is called extra-pulmonary TB.

Globally, TB is one of the top 10 causes of death and the leading cause of death from a single infectious disease. According to 2023 World Health Organization estimates, about a quarter of the world's population was infected with *MTBc*, of whom up to 10 million patients developed disease and 1.4 million died. Approximately 1.2 million (11 %) of TB cases occurred in children < 15 years old. The multi-drug-resistant form of the disease was responsible for up to 410,000 new cases per year (1), with an estimated 30,000 MDR/RR cases in children (2).

Belgium is a low incidence country for TB. This means that the annual incidence is below 10 new cases per 100,000 inhabitants. About 1000 new cases are diagnosed each year. However, the annual incidence in Belgium is higher than in its neighbouring countries with an incidence of 7,4 new cases per 100,000 in 2022 (3). TB in Belgium is characterised by a low transmission rate among the general population and small occasional outbreaks. The largest proportion of new TB cases in adults arise from reactivation in patients with TB infection (formerly called latent TB) (4).

The disease affects mainly (but not exclusively) groups living in precarious socio-economic conditions: homeless people, refugees without an income, (ex-)prisoners and people living in poverty (5). Likewise, recent contacts of contagious TB cases as well as professionals working with populations at risk or health care professionals have a higher risk of exposure and infection. The higher population density and the higher concentration of risk groups explain why cities such as Brussels, Antwerp and Liège have a higher incidence of TB (6).

About 1 to 2 % of all new TB cases are infected with a multi-drug-resistant strain. This rate is stable over the years in Belgium (6). However, it remains a serious public health threat and requires early diagnosis to contain spread, as its treatment is more complex than the treatment of regular TB, it's many times more expensive and may give more severe side effects.

In 2015, the WHO formulated the ‘end TB strategy’ (7) with 2 main targets for 2035: 90 % reduction in TB incidence and 95 % reduction in mortality from TB. To achieve this, early and universal access to diagnosis and treatment for all TB cases must be ensured. Financial and social protection as well as qualitative guidance for the TB cases are also important. This guideline will discuss the way that these international recommendations are implemented in Belgium.

Although TB incidence tends to decrease in Belgium, the control of TB remains an arduous task and the evolution of the TB epidemiology depends on multiple factors such as migration flows, living conditions in prisons and shelters, homelessness, the impoverishment of the population. For more information on TB epidemiology in Belgium, consult the TB register through the following websites: www.respiratoiregezondheid.be and www.fares.be/tuberculose.

2.1.2. Symptoms of TB disease “When to think of TB?”

The symptoms of TB vary according to the site of the disease and are usually nonspecific. Up to 50 % of patients with active TB are asymptomatic (8). The symptoms of bovine TB (active TB disease caused by *M. bovis*, entity of *MTBc*) are clinically indistinguishable from pulmonary TB. Classical or common symptoms of TB are:

- B-symptoms = weight loss, fever/chills, night sweats
- Unexplained persisting fever or failure to thrive in young children
- Consider pulmonary TB in case of:
 - Cough since > 2 to 3 weeks
 - Haemoptysis, especially in more advanced stages of the disease
 - Chest pain and dyspnea

These symptoms are even more suggestive of TB in case of epidemiological or individual risk factors: recent exposure, provenance from high-incidence country, immune suppression, comorbidities, ...

Symptoms of pulmonary TB can be less prominent in children below 10 years of age and in PLHIV or immunosuppressed (from any cause) patients. Teenagers (children as from 10 years old) and adolescents (14 years and older) may present with adult-type TB.

In extra-pulmonary TB, non-specific symptoms are usually present; a non-exhaustive overview is discussed in the chapter regarding diagnosis. The most frequent forms of EP-TB are lymph node TB and pleural TB, but the bacillus can cause disease anywhere in the body. EP-TB is more common in women, children and PLHIV or patient with other causes of immunosuppression (9), particularly meningeal TB. The forms most urgent to act upon in the youngest age group are miliary TB and meningitis (which can present with subtle signs of only lethargy or vomiting).

2.1.3. Contagiousness

The most common way of TB transmission is via inhalation of viable *MTBc* droplet nuclei, which are contained in the aerosol generated by pulmonary TB cases. Other transmission modes are rarely reported and should be considered of little relevance (e.g. milk ingestion, skin abrasion, sexual, congenital, ...).

The contagiousness of the patient depends on the concentration of tubercle bacilli in the sputum, the severity of the cough symptoms, the cough hygiene of the patient, the duration of exposure. Transmission occurs more easily indoors in rooms with suboptimal ventilation.

The risk of contagiousness is significantly higher in pulmonary (or laryngeal/pharyngeal) TB-disease with positive sputum smear prior to effective treatment initiation compared to culture-positive disease with negative smear. Extra-pulmonary TB-disease is not contagious in daily life settings. On the other hand manipulation of extra-pulmonary tissues by health care workers (pathologists, surgeons, ...) might generate aerosols and therefore, personal protection equipment is needed in those settings.

Young children rarely spread infection because they have usually a paucibacillary disease.

Sputum smear and culture can remain positive for more than two weeks after treatment initiation, however infectiousness drops very rapidly if adequate treatment is implemented (10).

Sputum smear microscopy is a surrogate marker of TB infectiousness; this has been demonstrated mainly prior to initiating therapy (11) (12). Smear negative cases are considered less infectious. Infectiousness depends not only on the presence of viable mycobacteria in sputum but also on cough dynamics. Epidemiological studies estimated that 8-16 % of TB infections are attributable to sputum smear-negative, but culture positive index cases (13).

2.1.4. Risk groups and risk factors (6)

The following groups are more likely to develop TB disease because they are more frequently exposed to the TB bacillus and/or have more risk factors predisposing to the development of an active disease.

- People coming from or with a long term stay in a country with high TB prevalence, including
 - Undocumented migrants
 - Asylum seekers
 - Visiting friends or relatives (14)
- (Ex-)Prisoners
- Homeless people
- Close contacts of contagious TB cases, young children being more vulnerable.
- Immuno-compromised people due to illness or treatment (e.g. patients with diabetes, immune suppressive treatment, etc.)
- PLHIV
- Patients experiencing substance use disorders, including those related to illicit drugs, alcohol, or tobacco consumption.

Risk groups for multi-drug resistant (MDR/RR)-TB are:

- People coming from or with a long-term stay in a country with high prevalence of multidrug-resistant TB. The incidence of TB and percentage of resistant cases for different countries can be found via the following website: <https://www.who.int/teams/global-tuberculosis-programme/data>
- Close contacts of people with pulmonary multi-drug-resistant TB
- Prisoners

- Health care workers
- People previously treated for TB while suffering from malabsorption due to illness or drug-drug interactions.
- People with previous TB treatment (especially if notion of poor compliance, inadequate regimen, medication stock outs, ...)

More information on risk factors or risk groups in Belgium can be found in the annual TB register which can be found on the website of Respiratoire Gezondheid (VRGT) and FARES.

2.2. Programmatic aspects of TB control in Belgium

To combat TB in a low incidence country as Belgium, we focus on several main interventions (4):

- Providing a performant and accessible health care system so that the passive detection and treatment of all TB cases can be guaranteed with minimal delays. Besides, extra attention and outreach activities might be organised for vulnerable groups.
- Active screening in specific risk groups. In Belgium this is performed in asylum seekers, prisoners and homeless people (15).
- Identifying patients with TB infection by investigating contacts and providing preventive treatment to patients who have been exposed to infectious persons (16).
- Ensuring quality TB surveillance and monitoring.
- Treatment supervision and social protection

Besides these key interventions, continuous medical education is provided maintain awareness and expertise in TB among healthcare providers and the general public.

On the websites of Respiratoire Gezondheid (VRGT) and FARES, trainings on TB for health care providers are available as well as statistics on TB in Belgium.

The main axes of TB control in Belgium are:

2.2.1. Universal access to TB care (diagnostics and treatment)

For patients with health insurance, reimbursement for TB diagnostic procedures and standard first-line treatment is covered by RIZIV/INAMI. FEDASIL is in charge of providing social protection to the asylum seekers and the Ministry of Justice is responsible for medical expenses of the prisoners. Reimbursement for undocumented migrants can be provided through the system of 'Dringende medische hulp' or 'Aide médicale urgente' provided by OCMW/CPAS. In exceptional cases, e.g. foreign students, EU employees ..., other (private) insurances may pay for the expenses.

However, not all TB costs (e.g. second-line medication) are covered by the different social security systems. Moreover, some patients cannot access any social protection or are unable to pay the out-of-pocket expenses. The BELTA-TBnet project (funded by RIZIV/INAMI) provides a reimbursement system for these exceptional cases. BELTA-TBnet also takes care of the

reimbursement of imported TB medicines in case of medication stock-outs or for MDR/RR-treatment regimens. More information on www.belta.be.

Besides, RIZIV/INAMI also funds the BELTA-DOT project, supporting Respiratoire Gezondheid (VRGT) and FARES nurses to ensure a patient-centered care with additional support if needed, based on the principle of case management approach.

2.2.2. Surveillance and notifications of TB-cases

Prevention, surveillance and control of infectious diseases, including TB, are organised at regional level.

- Any TB case - confirmed or presumed - must be notified to the regional authority.
- Any positive bacteriological examination is notified by the laboratories.

The treating physician must report the case when TB is diagnosed. This is also required if treatment is initiated, based on clinical suspicion, without microbiological confirmation of TB. Reporting is mandatory within 24 or 48 hours from the first suspicion, depending on the region.

The reason for notification is that contact tracing and appropriate patient follow-up can be organised adequately and timely. Surveillance also ensures the rapid control of TB outbreaks and a better understanding of the epidemiological context.

FOR MORE PRACTICAL INFORMATION, PLEASE REFER TO THE CHAPTER 8 “PRACTICAL ASPECTS”, PAGE 81.

2.2.3. Contact tracing

In Belgium contact tracing is a responsibility of the regions and is organised in collaboration between the regional authorities and Respiratoire Gezondheid (VRGT) and/or FARES, after a new TB case is identified. In some settings (schools, prisons, asylum centres etc.) the medical services of these structures can also seek the help of Respiratoire Gezondheid (VRGT) and/or FARES. The modalities of contact tracing are discussed in the Belgian guidelines on TBI diagnosis and management (16).

Contact tracing identifies people who have been in contact with an infectious TB patient and who may have contracted TB infection or developed TB disease. If the index patient is a child, contact tracing tries to find the source of the young TB patient.

2.2.4. Contamination prevention: isolation, masks and cough hygiene

For an infectious patient, several actions can be applied to prevent further infections. These include isolation, wearing a mask and cough hygiene.

Isolation is initiated from the time an adult or child is suspected of having infectious TB, most of the time in a hospital setting.

All facilities that admit people with infectious tuberculosis need a clear protocol outlining the necessary infection control procedures. This protocol should mention the use of high-quality masks and FFP2 respirators, HEPA-filters, negative pressure rooms, UVGI ...

In case of isolation in a hospital setting, the minimal requirements for adequate infection prevention are:

- The patient is isolated in an individual room with closed door and limited visits
- Adequate ventilation, the recommended minimum number of air changes per hour is 12 (17).
- Family and health care workers when visiting the patient should wear an FFP2 respirator, as personal protective equipment.
- Children under the age of 5 should not visit the patient.
- In case of (suspected) multi-resistant germ, a room with negative air pressure is recommended.
- When the patient must leave the room for a medical exam, he/she must wear a surgical mask while the medical staff in charge of the exam must wear an FFP2 respirator.
- If a child is isolated in hospital, it is essential to ensure that accompanying adults are not contagious, as they may be a potential source of contamination for young patients or the staff of the paediatric ward.
- If a patient has recently given birth or is breastfeeding, mother and child remain together unless the mother has MDR/RR-TB; in such cases, separation during the first two weeks can be considered with shared decision making. Breast milk may be expressed during this period. The child should receive preventive treatment if active TB is ruled out. *MTBc* transmission via breast milk is unlikely: milk from mothers with susceptible TB is safe, and likely also with resistant TB, but use should be based on expert advice and shared decision making.
- In ambulant care setting it is recommended to ventilate the room after the visit of a (presumably) infectious patient. Ensure that windows remain open and close the room's doors for a minimum of two hours before re-entering the room. If the room must be used without possibility of adequate ventilation, the staff should wear an FFP2 mouth mask.

Isolation duration (18, 19, 20) depends on initial microbiological findings, considering smear and culture positivity and DST results. We summarise the recommendations of the Belgian superior health council (18, 19) in [table 1](#).

If the index patient is a child with no adult-type TB: the risk of contagiousness is probably very low and isolation measures are probably not required, although there is no consensus on this.

Table 1: Recommendation of isolation based on microbiological results

	Susceptible TB	MDR/RR-TB
Smear negative/Culture negative or unknown	15 days of treatment and clinical and/or radiological improvement	Not applicable
Smear negative/culture positive	15 days of treatment and clinical and/or radiological improvement	3 consecutive negative cultures**
Smear positive / culture positive	clinical and/or radiological improvement* ideally confirmed with 3 consecutive negative smears (but this microbiological proof is often not feasible if patient has no productive cough) with at least 15 days of treatment	3 consecutive negative cultures**
* In case of initial positive smear obtained by BAL, end of isolation will be based on clinical and radiological evolution. In most situations there's no need to repeat the BAL.		
** If still sputum available, often not feasible if patient has (no longer) productive cough.		

While hospitalisation is ideal during initial treatment, home airborne isolation may be possible if certain prerequisites are met.

- The patient is not affected by a presumed or confirmed resistant form of TB.
- The patient shows clinical improvement.
- The patient is likely to comply with his/her treatment and follow-up
- There is good communication between treating physician, general practitioner, FARES/ Respiratoire Gezondheid (VRGT) and other involved partners to ensure adequate follow-up.
- The patient agrees to stay at home as long as he/she is considered infectious and is committed to wearing a surgical mask when going out, especially for follow-up medical visits.
- The patient is not living with children < 5 years or immunocompromised persons
- The immunocompetent people living with the patient were already in contact with the patient prior to treatment initiation.
- Contact screening is ongoing.
- The patient is not living in a community

In case of infection with an MDR/RR-strain, isolation criteria are stricter. Isolation can be stopped if culture conversion is obtained in a patient with a positive clinical evolution, good compliance and ideally radiological improvement. Microbiological confirmation however is not always possible if the patient has no (longer) productive cough. In case of patients living in community housing or co-living with young children, the criteria are usually stricter and 6 consecutive negative smears and 3 consecutive negative cultures are ideally provided, although this is not feasible in all patients. Of course, this should be evaluated on an individual basis and is preferably discussed with different stakeholders, i.e. first-line caregivers, specialists involved in treatment management and national MDR-TB Expert Group.

EPIDEMIOLOGY, SYMPTOMS, RISK FACTORS:

Key points

1. TB affects mainly the lungs and in the Belgian context is more prevalent in people living in precarious socio-economic conditions.
2. Multi-drug-resistant strains are responsible for 1-2 % of the TB cases in Belgium.
3. To prevent TB transmission, knowledge about symptoms of the disease is important as early diagnosis can prevent further transmission.
4. Public health organisations Respiratoire Gezondheid (VRGT) and FARES play a central role in training on TB as well as in contact tracing and management of TB cases, this in collaboration with the local health authorities and treating teams.
5. Transmission prevention measures help also in reducing TB-incidence.

3. Diagnosis

Generally, a diagnostic procedure should start as soon as there is a clinical and/or epidemiological suspicion of TB. TB often causes non-specific symptoms, which can vary greatly, depending on the TB sites (pulmonary and extra-pulmonary).

The diagnostic approach consists of targeted laboratory testing and medical imaging procedures.

Even in the absence of microbiological confirmation, TB can be considered - and treatment initiated - in case of high clinical/radiological probability provided alternative aetiologies are being/have been ruled out.

The medical follow-up requires multidisciplinary management which also includes repeated laboratory tests to check the response to treatment.

3.1. Diagnosis of pulmonary TB in adults and adolescents (≥ 15 years)

This is the most frequent form of TB (70-75 % of cases in Belgium). Early diagnosis is important to limit the transmission of TB. It is based on the following factors: clinical presentation, medical imaging, microbiology exams ...

Clinical presentation of TB was discussed previously in this guideline ('when to think of TB'). One should consider TB in case of a persistent pulmonary infection or fever that does not respond to standard antibiotic therapy.

It is hard to make a differential diagnosis with other diseases based on the clinical presentation alone. Other tests are necessary to differentiate.

3.1.1. Medical imaging

Radiological images of TB can take on different appearances, some of which may be atypical, especially in immunocompromised patients. When available, it is helpful to compare with imaging performed previously. While younger children will more often present with intra-thoracic lymph node enlargement or miliary TB, pulmonary TB in teenagers/adolescents, like in adults, will often present with cavitation(s) and pleural effusions.

The algorithm (**Figure 1**) sets out the procedure to be followed based on imaging findings:

- Any abnormality compatible with TB constitutes a suspicion of the disease; microbiological confirmatory tests should be requested.
- If a chest X-ray shows non-specific lesions in a patient at risk of TB and/or clinically suspected of TB, microbiological tests should be requested and chest CT scan performed.
- If chest XR is normal in a patient at risk of TB and with clinical suspicion, the following tests are recommended in addition to microbiological work-up: perform a chest CT scan and if the latter is not conclusive, ensure clinical and radiological follow-up after 1 to 2 months.

3.1.2. Microbiological tests on respiratory samples

Microbiological tests on respiratory samples confirm TB by detecting tubercle bacilli and help determine a patient's infectiousness for contact tracing purposes (16).

These tests must be carried out if there is a clinical or radiological suspicion of pulmonary TB. Several microbiological tests are available:

- direct microscopic exam, also called smear
- PCR (often combined with screening for rifampicin resistance and occasionally also for isoniazid resistance). PCR identifies DNA of *MTBc*, is more sensitive than direct smear and quickly available compared to culture. The rapid PCR-based test for RMP-resistance is recommended at time of diagnosis: a quicker detection of resistance allows an early start of appropriate MDR/RR-TB treatment. In Belgium reimbursement for molecular tests for *MTBc* is limited to 3 samples per year and restricted to specific criteria (no antibiotics > 7 days prior to the test and minimum 1 out of 3 of the following: positive smear, radiological or clinical suspicion of TB, invasive (bronchoscopic, puncture fluids, biopsies) sample).

It should be emphasized that a positive PCR result does not necessarily indicate ongoing disease, as the assay may detect residual mycobacterial DNA even after successful treatment. For this reason, routine monitoring of PCR during therapy is not recommended unless there is suspicion of treatment failure.

- culture of mycobacteria remains the gold standard. Once the culture is positive, species identification is performed, followed by DST if *MTBc* bacilli are detected.

Sputum smear and culture are carried out on (a maximum of) 3 qualitative sputum samples (PCR usually is only performed on one). The samples are collected preferably in the morning, one day apart. Sputum should be collected in sufficient quantity (5 to 10 mL) in sterile jars and must be transported under optimal conditions (plastic jar marked with the patient's name, tight-fitting lids, packaging to prevent breakage), with a thoroughly completed and identified laboratory request form, including correct patient identification. Samples should be transported to the laboratory without delay, otherwise they should be stored in the refrigerator between 2° and 8°C. In the absence of sputum, it is up to the specialist to decide whether it is appropriate to use alternative techniques:

- sputum induction using an aerosol of hypertonic saline solution (usually 3 - 4,5 % concentration) (21);
- bronchial (or bronchoalveolar) lavage by bronchoscopy (or gastric lavage in children)

The algorithm (**Figure 1**) sets out the follow-up strategy depending on the results of the microbiological tests. Even if the results of smear and PCR are negative, anti-TB treatment may be prescribed while awaiting the results of the culture, in cases of strong radio-clinical suspicion or based on specialist advice.

3.1.3. Role of other tests in the diagnostic work-up

Medical imaging

A thoracic CT scan is recommended in the following situations:

- Radiographic findings indicate TB, but without microbiological confirmation.
- Normal chest X-ray and negative microbiological tests in a patient with clinical signs strongly suggestive of TB (especially in patients at risk for TB).
- In case of lymph node enlargement, especially if not associated with pulmonary TB.
- Suspected miliary TB (Chest XR may be sufficient, especially in children).
- Suspicion of concomitant thoracic malignancy.
- MDR/RR-TB.

Immunological tests for TB infection

1. Tuberculin skin test

This test is used to diagnose TB infection (formerly called latent TB) and does not distinguish infection from (active) TB disease. It should not be used systematically if pulmonary TB is suspected in adults. However, if positive (and even more so if there is a conversion), a TST can provide additional support and contribute to the diagnosis of the disease. A false negative result is possible in immuno-compromised patients, in early infections and in cases of severe TB.

For more information on this test, see the document entitled 'Belgian guidelines on the Diagnosis and Management of tuberculosis infection' at www.fares.be or www.respiratoiregezondheid.be.

2. IGRA

These tests are performed on blood and have not been validated on other samples. They test the in vitro release of interferon- γ by T cells following stimulation by *M. tuberculosis*-specific antigens. BCG vaccination has no influence on IGRA results. Available commercial tests include QuantiFERON-TB Gold In-Tube® and T-SPOT.TB®.

Like the TST, they do not distinguish between (latent) TB infection and (active) TB. They are therefore of limited use in diagnosing symptomatic pulmonary TB.

Blood test

There are no specific blood tests available to confirm diagnosis of (active) TB. Elevated inflammatory parameters (e.g. CRP, ESR) are often seen in case of TB but are not specific for this disease. On the other hand, it is important to note that absence of elevated inflammatory parameters doesn't exclude the diagnosis of TB (22).

In case of miliary TB it is worthwhile to perform haemocultures using specific vials for Mycobacteria.

Endoscopic bronchial procedures

1. Bronchial or broncho-alveolar lavage

This invasive test can be considered in the presence of a strong suspicion of TB when smear and PCR for *MTBc* are negative or in the absence of sputum. This examination should only be carried out under strict conditions of personal protection. The respiratory secretions collected are subjected to microbiological testing (smear, PCR and culture for mycobacteria).

In children, BAL can improve sample quality but does not significantly increase diagnostic yield (23). In young children sampling gastric fluid gives the most optimal yield in diagnosis, with even a better diagnostic yield by combining gastric lavages and BAL.

2. Transbronchial biopsies

Can be performed during bronchoscopy. Histopathologic examination can reveal granuloma formation in the lung parenchyma. These samples (fresh sample in NaCl 0,9 % solution, not fixed in formalin solution) should be systematically sent for microbiological testing (smear, PCR and culture for mycobacteria).

3. Transcarinal puncture, EBUS, EUS

This procedure can be performed in case of mediastinal lymph node enlargement with suspicion of intra-thoracic lymph node TB. This examination is preferred to the excessively invasive mediastinoscopy. Samples should be sent both for cytological/histological analysis (fixed in formalin solution) as well as for microbiological testing (smear, PCR and culture for mycobacteria; fresh sample in NaCl 0,9 % solution instead of fixed in formalin solution).

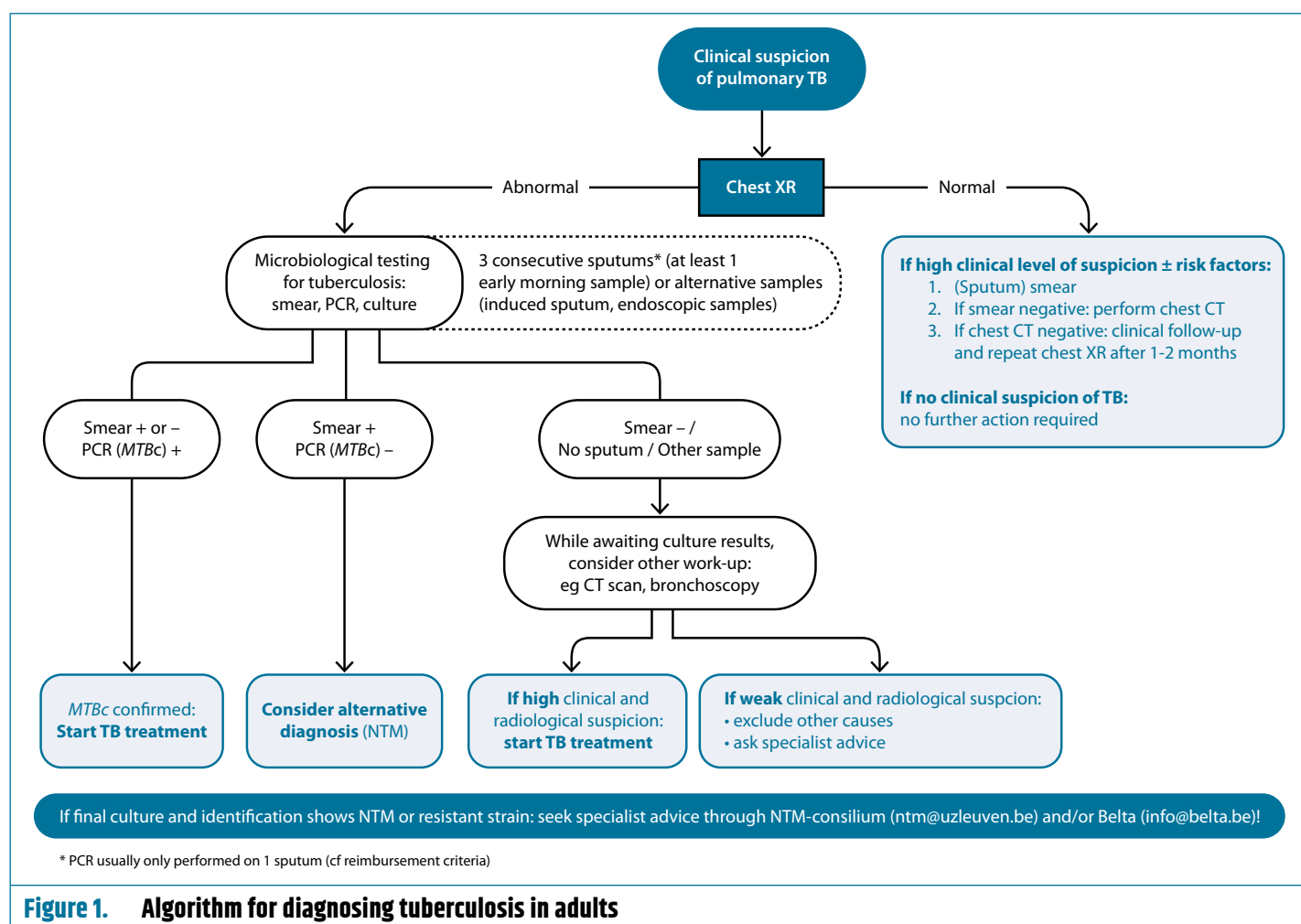


Figure 1. Algorithm for diagnosing tuberculosis in adults

3.2. Diagnosis of extrapulmonary TB in adults and adolescents (≥ 15 years)

The most frequent forms of extra-pulmonary TB in Belgium are pleural and lymph node TB.

In addition to histological examination, which only gives a presumptive diagnosis, a **culture must always be performed on the sampled material** (fresh sample, not formalin fixed) to obtain microbiological confirmation of the disease, which is of utmost importance to perform DST.

Table 2 discusses the clinical manifestations of extra-pulmonary TB and the proposed diagnostic tests.

System	Most common symptoms	Most frequent localisation	Diagnostic work up
Respiratory	Dysphonia, otalgia, odynophagia Breathing pain, dyspnea	Upper respiratory system Pleural	Sputum, laryngoscopy ± biopsy Thoracocentesis (liquid in dry sterile tube), pleural biopsy (sterile tube with saline)
Dermatological	<u>Scrofuloderma</u> : fistulisation of underlying lymph node <u>Lupus vulgaris</u> : plaque with verrucous edge – ulceration is possible	Mainly in the neck, axilla, groin Mainly in the face	Fine Needle Aspirate and/or biopsy (sterile tube with saline)
Ophthalmological	Red eye, ophthalmalgia, visual impairment; often in episodes	Uvea	Referral to ophthalmologist for fundoscopy and possibly sampling of anterior chamber fluid or vitreous humour, although often sample too small to perform PCR.
Cardiac	Often asymptomatic; in case of symptoms: dyspnea, chest pain, tamponade	Pericardium	Cardiac ultrasound, CT scan Image-guided biopsy or pericardiocentesis
Neurological	Headache, nuchal rigidity, confusion, epileptic attacks, blindness, focal nerve deficit ...	Meninges Cerebral	MRI, Lumbar puncture (6-10 mL of CSF, centrifugation needed)
Gastroenterological	Pain and swelling in right upper quadrant Diarrhoea Chronic abdominal pain	Liver Intestinal, peritoneal Generalised in abdomen	Ultrasound, CT, endoscopy Image-guided biopsy or endoscopic biopsy, ascites puncture
Lymphatic	Mostly unilateral, non-painful gland swelling - sometimes fistulisation Bronchial compression (mainly seen in children)	Extra-thoracic lymph node (often cervical) Intra-thoracic lymph node	Biopsy or aspirate of pus, if needed image-guided EBUS-guided biopsy

Table 2: Clinical presentations of extra-pulmonary TB

System	Most common symptoms	Most frequent localisation	Diagnostic work up
Nephrological	Dysuria, pollakiuria, haematuria or sterile pyuria	Kidney	Culture on complete morning urine, no transfer in urine tube (40 mL minimum; 3 samples of urine over 3 consecutive days)
	Adrenal insufficiency: hypotension, hyponatremia, normal to high potassium, hypoglycaemia, increased uraemia	Adrenal glands	Ultrasound, CT, pyelography: US/CT-guided biopsy Image- or EUS-guided biopsy
Genital	Sterility, extra-uterine pregnancy, tenderness during genital examination	Salpinx	Ultrasound, CT Image-guided biopsy
	Chronic pain, scrotal swelling	Epididymis	
Musculoskeletal	Vertebral collapse, radiating pain, kyphosis	Vertebra, discus (Pott disease), psoas muscle	XR, CT or MRI Biopsy Articular fluid
	Chronic pain, osteomyelitis	Bone	
	Mono-arthritis	Knee, hip	
Miliary	B-symptoms, lethargy		Haemocultures in dedicated vials, e.g. BACTEC™ Myco/F Lytic Culture Vials NO ordinary HC bottles

3.2.1. Microbiological testing

As for pulmonary TB, it's important to obtain microbiological confirmation of extra-pulmonary TB. Following tests should be performed systematically on any sample taken in a patient with suspected extra-pulmonary TB: direct microscopic examination and culture for mycobacteria. The culture will enable DST. Additional performance of PCR on a primary sample should be discussed with a TB-specialist and a microbiologist. Although this test is not thoroughly validated for non-respiratory samples, it may still be helpful in some cases, such as biopsies showing granuloma possibly attributable to *MTBc*.

Testing for *MTBc* can be carried out on any type of suitable sample: pleural effusion, first morning urine (40 mL minimum; 3 different samples over 3 consecutive days), cerebrospinal fluid (ideally 10 mL, minimum 6 mL), biopsy, lymph node or abscess pus, blood cultures for mycobacteria, etc. It is important to send fresh biopsy tissue for mycobacterial culture and PCR. Swabs or formalin fixed biopsies are not suitable for *MTBc* culture.

The quantity collected must be sufficient to carry out the required tests. Large volumes of fluid are needed also for CSF (see [table 4](#)), for instance a minimum volume of 1 mL is needed to perform a GeneXpert test. Collection, transport and storage conditions are like those recommended for pulmonary TB.

3.2.2. Role of other tests in the diagnosis of extra-pulmonary TB

Biopsy sample is often justified in this context. The sample will be subjected to histological examination: presence of granuloma with a necrotic centre and Langhans cells is suggestive for TB-disease, but this is not specific for TB. Performance of microbiological tests in parallel is of utmost importance to confirm the diagnosis of TB with certainty and once confirmed to perform resistance testing. Therefore, we underline the importance of sending also a fresh sample (biopsy in physiological saline solution = NaCl 0,9 %) for the microbiological part of testing.

Molecular biology tests on clinical samples (using nucleic acid amplification such as PCR) may be considered as an additional examination in extra-pulmonary TB where bacteriological confirmation is difficult. Despite its suboptimal sensitivity (risk of false negatives), this type of test is recommended as an additional diagnostic argument, even in paucibacillary cases, to increase the chances of confirming TB.

However, commercial tests are only approved for respiratory samples. Moreover, the presence of blood (or other nucleic acid amplification inhibitors) in the sample may cause uninterpretable results.

The rapidity in obtaining results from a molecular test (within a few hours) is particularly useful in severe forms of TB such as meningitis, but **a negative result does not rule out the diagnosis**. In that regard, the clinical presentation and evolution of the patient is decisive and it is preferable to start an unnecessary TB treatment than to start it too late.

If positive, this highly specific test makes it possible to distinguish between tuberculous and non-tuberculous mycobacteria, which is particularly useful for extra-thoracic (mainly cervical) lymph node enlargement.

Imaging techniques such as CT, MRI, ultrasound may be indicated in certain forms of extra-pulmonary TB as described in [table 2](#). MRI is mainly indicated in case of osteomuscular or neurological presentations of TB.

Immunological testing such as **TST and IGRA** were discussed also in the paragraph on pulmonary TB.

The tuberculin skin test can be helpful, especially in the presence of a (recent) conversion. As mentioned before, **it does not distinguish between TB infection and active disease**. However, it can provide an additional argument for the diagnosis of extra-pulmonary TB, which is often more difficult to diagnose than pulmonary TB.

Same is true for IGRA (Interferon Gamma Release Assay) tests: they are of little use in the diagnosis of pulmonary TB, but they can be useful in the diagnosis of extra-pulmonary TB (e.g. ocular TB) where any additional argument in favour of the diagnosis is important.

Nevertheless, a negative TST and/or IGRA does **not** exclude active disease (24).

Blood tests are not helpful in confirming the diagnosis. Of course, they do matter to determine impact of TB at the organ level (e.g. liver involvement).

3.3. Specific aspects of TB-diagnosis in children

In children (0-14 years), the risk of developing TB disease following exposure is age-related (see [table 3](#)), with the cumulative risk being higher in children under 5 and adolescents (>14 years).

Children younger than two years old are at a very high risk of developing severe disease during the first year following exposure to the infection. The clinical presentation in those children is often acute without significant prior symptoms. Children aged 5-10 years progress rarely to active disease and might present with suggestive TB symptoms. Over 10, there is again a period of increased susceptibility to TB, with an important increase in the prevalence of TB infection and TB disease incidence.

Table 3: Forms of TB and risk of disease (%) in infected children, according to age

	< 1 year	1-2 year	2-5 year	5-10 year	> 10 year
No active TB	50 %	70-80 %	95 %	98 %	80-90 %
Pulmonary TB	30-40 %	10-20 %	5 %	2 %	10-20 %
Meningeal or Miliary TB	10-20 %	2-5 %	0.5 %	< 0,5 %	< 0,5 %

In paediatric practice, most cases are identified actively during contacts' screening around a TB patient or during targeted screening of newly arrivals from high endemic countries. These cases are often non-symptomatic, with a non-severe form of the disease. Outside this context, the diagnosis of TB is based on symptoms or clinical/radiological abnormalities suggestive of the disease. Under these conditions, TB involvement is usually more extensive. Identifying the infectious adult is crucial here.

A specific form of TB in children is the congenital TB. As it is very rare in Belgium, it will not be discussed in this document, but we recommend referral to a paediatrician with a specific expertise in domain of TB.

Whatever the context, the diagnosis of TB in children requires:

- A rigorous assessment of the risk of infection (proven or highly probable contact with a contagious adult or notion of a high-risk environment).
- The recognition of clinical signs: the classic symptoms of adult TB (cough, haemoptysis, weight loss, etc.) are rarely seen in young children, and occasionally in older children or adolescents. More than half of children under the age of 15 may have no (or very few) symptoms ('silent disease'), even when radiological abnormalities are present.
- The analysis of chest X-ray images (specifically hilar lymphadenopathy) ideally interpreted by paediatric infectiologist with expertise in TB or the results of other tests performed, if an extra-pulmonary TB is suspected.
- The result of the TST which should be interpreted by specific, standardised criteria (16). Although TST does not distinguish disease from infection, it is sometimes useful in children, given the difficulty of making a bacteriological diagnosis of TB. The same considerations apply to IGRA tests.

3.3.1. Microbiological results

Given the paucibacillarity of the lesions, it is important to take multiple samples. In the absence of sputum, gastric lavage remains the technique of choice (except if gastric feeding through tube) for collecting pulmonary secretions (minimum 3-4 mL; the larger the volume, the greater the sensitivity). Even in the absence of pulmonary lesions on chest imaging, this test may still be positive. In that regard, a low threshold for performing gastric lavage, including when suspicion of extrapulmonary TB, is warranted. Establishing a well-defined protocol for gastric lavage is essential, ensuring that nurses, clinicians, and the microbiology laboratory follow clear procedures. PCR and culture can also be performed on stool samples. However, PCR is often impractical because other stool contents can interfere with the results. For children aged 10 years and above, sputum induction can serve as an alternative diagnostic method.

Studies have shown that diagnostic yield improves when samples are taken from multiple sites. Collecting these samples on the same day can enhance feasibility and reduce logistical constraints (25).

In extra-pulmonary TB, other samples might be collected and sent for direct examination, culture, and, when appropriate, pathological analysis. The molecular biology testing (including PCR) as additional tool is fully justified.

While awaiting the results of the child's culture and DST, all efforts to get a respiratory sample of the index person (suspected of being the source of contamination) should be made, in order to establish the epidemiological link between the child and the suspected index case and to adapt the treatment regimen in case the strain of the index case is resistant. Strain typing by WGS can be performed in the national reference lab if the cultures of the child and the index case are positive. If a cluster is confirmed, it will be notified to Respiratoire Gezondheid (VRGT)/FARES.

3.3.2. General consideration in children

In practice, in non-endemic countries like Belgium, the diagnosis of TB in a child should be considered in the presence of the following triad:

- suggestive clinical signs and/or suspicious radiological images
- contact with a contagious adult
- positive immunological test for TB infection (TST and/or IGRA). Absence of immunological signs, on the other hand, by no means, precludes the diagnosis

Depending on the evidence available, the diagnosis may be classified as follows:

- Possible TB
- Probable TB: exposure to index case with TB, clinical/radiological signs and positive immunological test for TB infection (TST and/or IGRA)
- Confirmed TB: microbiological confirmation

In children, 50 % of cases with active TB will never be confirmed on microbiology. It will be a clinical diagnosis.

3.4. Specific features of diagnosing TB in PLHIV

The clinical presentation is often atypical. Extra-pulmonary TB is common (lymph nodes are involved in about one quarter of cases) (26) and is often associated with pulmonary involvement. Miliary TB may present with a normal chest XR.

The multiplicity of clinical forms and the frequency of extra-pulmonary involvement mean that biopsy and/ or liquid samples must be taken for histological and microbiological diagnosis. Since PLHIV often have disseminated TB, in a clinically suspect patient with a prolonged febrile episode, collection of blood cultures (or possibly marrow cultures) in designated vials should be considered. The presence of acid-fast bacilli in PLHIV indicates usually an infection with *MTBc* if the patient has lived in a high TB prevalence country. In patients from low TB prevalence country, infection with non-tuberculous mycobacteria (NTM) should be considered. If a patient presents with severe general health deterioration, sweating and a (long-lasting) febrile syndrome without an established diagnosis after a full work-up, the possibility of TB should be raised, even in the absence of microbiological evidence, and may justify an empiric treatment.

3.5. Practical Aspects

3.5.1. What are the steps in diagnosing pleural TB?

This is also applicable to children (usually of > 5 years old)

- Perform a frontal and lateral chest XR and eventually a thoracic ultrasound
- Systematically request a sputum smear (or gastric lavage)
- Perform a pleural puncture and systematically request:
 - Biological and chemical analysis of the pleural fluid
 - > Initially polynuclear exudate, which becomes lymphocytic at > 90 % (more than 10 % eosinophils does not support the diagnosis)
 - > Protein > 3 g/100 mL (> 5 g/100 mL in 50-77 % of cases)
 - > LDH > 500 IU/L in 75 % of cases
 - > Decreased pH
 - > Pleural glucose/serum glucose < 0.5
 - Microbiological analysis
 - > Smear positive (< 30 % of cases)
 - > Mycobacteriological culture positive in ± 42 % of cases
 - > PCR should be considered: however false negative results are common.
- In the absence of an immediate diagnosis, take a pleural biopsy (3 to 4 fragments) (in children this is performed exceptionally).
 - > The presence of granulomas clearly points to the diagnosis, especially in case of caseating granuloma.
 - > Culture the biopsied material systematically (positive in ± 60 % of cases)

3.5.2. What are the steps in diagnosing extra-thoracic lymph node TB?

To make a differential diagnosis with malignant causes (e.g. lymphoma), infection with non-tuberculous mycobacteria (NTM) or cat scratch disease, the following examinations are required:

- Perform a chest XR to ensure that there are no lung lesions. If any, look for *MTBc* in sputum or gastric lavage.
- In case of fistulisation, perform a direct examination and culture of the drainage fluid (aspiration via syringe, do not use swabs as they are not suitable for TB diagnosis), PCR on the puncture fluid may also be considered.
- Ultrasound followed by puncture if fluid content is present in the adenopathy. Perform the puncture from superior to inferior, to avoid fistulisation.
 - Confirmation of diagnosis: by systematic search for *MTBc* in the aspiration fluid (smear and culture). PCR may be considered as an additional test.
 - Presence of abundant lymphocytes in the aspiration fluid and/or giant cells are highly suggestive of TB diagnosis.
- Perform a biopsy or lymph node resection if the ultrasound does not confirm the fluid content or if the puncture is inconclusive.
 - Histological examination of the tissue: presence of (caseating) granulomas?
 - Always perform microbiological testing: smear, culture for mycobacteria; PCR may be useful
- If clinically indicated, a CT scan can be performed to check for other sites of lymph node involvement.

In non-endemic areas for TB, the hypothesis of infection by non-tuberculous mycobacteria (NTM) should be raised in the presence of cervical lymphadenitis, in children.

3.5.3. How is CNS-TB diagnosed?

In general, children under the age of 5, and more specifically those under the age of one, are at greater risk of developing CNS-TB compare to other age groups (see [table 3](#)). Meningitis occurs in 20-30 % of the miliary TB cases and is generally fatal in the absence of treatment. Every effort must be made to diagnose TB meningitis as quickly as possible:

- First, one should think about it! This is not so easy, because The clinical presentation of TB meningitis is similar to that of other central neurological diseases and varies widely clinically: acute, sub-acute or chronic; febrile or not; with or without signs of intracranial hypertension; associated with a sudden or progressive neurological deficit, with or without neck stiffness ... In a child under the age of 5 presenting with unexplained fever after exposure to TB, testing for TB-meningitis should be performed with a very low threshold. In any child below 1 year of age presenting with signs of active TB-disease (irrespective of meningitis signs), testing for TB-meningitis should be performed, as part of the workup.
 - If possible, when it is safe (location of granuloma might be on obstacle to perform a safe procedure), perform a lumbar puncture and perform a biological and chemical analysis of the CSF. The following triad is suggestive for TB:
 - > lymphocytic hyperleukocytosis ($10-500/\text{mm}^3$)
 - > high proteinorachy ($> 0.45 \text{ g/L}$ and often $> 1 \text{ g/L}$)
 - > hypoglycorrhachia (can be severe: $< 2.2 \text{ mmol/L}$)

However, at an early stage of the disease, neutrophils may dominate the CSF or even, CSF exams can be normal. As well in case of CNS tuberculomas/abscesses without meningitis, CSF exams may be normal.

Repeated lumbar punctures and CSF examination increase diagnostic yield (27). The volume of CSF needed is 6-10 mL. For neonates and infants tapping these large CSF volumes might be unacceptable. By centrifuging the sample, concentration of bacilli in the pellet may increase (28). **Table 4.** lists CSF volumes that can be tapped safely.

- The microbiological examination can confirm the diagnosis by demonstrating the presence of tubercle bacilli; however, smear and culture are rarely positive (and require a minimum of 10 mL of fluid as mentioned before). MGIT culture of CSF has a low sensitivity of 25-70 %, mainly due to too low volumes of CSF but has the advantage of allowing for extensive drug-susceptibility testing (29).
- PCR, if positive, enables a rapid diagnosis and can be performed on a small quantity of CSF. It should be performed first on the concentrated pellet and in case it is negative, repeat the test in the non-centrifuged CSF.

Given the importance of a correct diagnosis, we describe more in detail the optimal management of CSF-liquid: if a large CSF volume is available, first set aside 0.7–1 mL and centrifuge the remaining sample. Discard the excess supernatant that is not required for testing, taking care not to disturb the pellet. The remaining volume (pellet plus supernatant) should equal the sum of 0.7–1 mL for GeneXpert MTB/RIF or Ultra PCR, 0.5–2 mL for MGIT culture. Finally, resuspend (vortex) the pellet with the remaining supernatant. From this suspension: use 0.5–2 mL for culture, use 0.7–1 mL for PCR (GeneXpert MTB/RIF or Ultra), diluting with buffer solution to obtain a total of 2 mL. If the PCR is negative, repeat on the non-vortexed sample that was set aside, after adding buffer solution.

The procedure described above applies to the GeneXpert MTB/RIF or Ultra tests. Other commercially available PCR methods might require different procedures. As well with an in-house PCR, different volumes may be required. Real-time PCR in a cartridge-based system (like GeneXpert) has a better performance than culture and requires only 1 mL of fluid. A negative result doesn't rule out TB-diagnosis. Rapid PCR-based resistance testing if positive is very helpful in detecting timely MDR/RR-TB meningitis, which carries a high risk of mortality.

Table 4: Estimates of CSF production rate, total CSF volume and safe CSF volume taken for different age groups

	Mean CSF production (mL/h)	CSF volume (mL)	Safe CSF volume to take at LP (mL)
Adult	22	150-170	15-17
Adolescent	18	120-170	12-17
Young child	12	100-150	10-15
Infant	10	60-90	6-9
Term Neonate	1	20-40	2-4

- Carry out a magnetic resonance (MRI) scan as part of the radiological work-up to identify any tuberculomas or brain abscesses and determine the extent of the lesions. MRI is preferred to CT. MRI is also used for the follow-up of tuberculomas and abscesses: a loss of T2 signal (lesions evolving from white to black/grey) is observed in case of a favourable treatment response, including in IRIS (immune reconstitution inflammatory syndrome) lesions responding to immunomodulating therapy, while the T2 signal persists (white lesions) in treatment failure.
- Look for TB-disease in other sites with radiology or samples (sputum, gastric tubing in children, blood cultures, etc.) as meningitis can be a complication of miliary TB.
- Testing for TB infection, namely with tuberculin skin test and/or Interferon Gamma Release Assay (IGRA), have low sensitivity in TB meningitis (just above 50 % in children) (30).
- If CNS-TB is suspected in children, it is worthwhile to screen close contacts for TB, as this may offer clues for TB-exposure. This can help to make a presumptive diagnosis.

3.5.4. What is the time needed to obtain the results of the various microbiological tests?

Direct microscopic examination = smear (performed systematically): result within 24 working hours.

Culture and identification (performed systematically): depends on bacterial load, a higher bacterial load leads to earlier positive culture.

- on solid medium: negative after 8 weeks
- on liquid medium: negative after 6-8 weeks.

PCR: depends on the technique used and the workflow of the local laboratory.

- GeneXpert (MTB/RIF) assay takes 2 hours; unless you liaise with your microbiology laboratory or if the test is not available on-site, this may in take up to 24 working hours.
- Other PCR-techniques: to check with manufacturer or local lab.

DIAGNOSIS OF TB:

Key points

1. Always consider the diagnosis of TB in clinically suspect 'at risk' patients.
2. Regardless of the type of sample taken, microbiological tests (smear, PCR and culture for mycobacteria) should be systematically requested to confirm TB.
3. On positive smears, PCR should be performed on the first positive sample to distinguish between MTBc and non-tuberculous mycobacteria.
 - If positive, repeat PCR testing is not indicated.
 - If MTBc is confirmed by PCR, rapid genotypic testing for rifampicin resistance should be performed to obtain a quick diagnosis of MDR/RR-TB (see chapter on diagnosis of resistance to anti-TB drugs).
4. Biopsy material must be subjected to histological and microbiological examinations. For this type of material, it is important to collect samples both in saline and formalin solution.
5. In the presence of extra-pulmonary TB, a systematic search must be made for co-existing pulmonary disease.
6. Diagnosis of TB in young children requires vigilance because:
 - they are more likely to develop severe or even fatal TB
 - the time between TB infection and disease can be very short
 - it is a «sentinel» event: a very good indicator of recent transmission.

In children, think of TB when the following triad is present: contact with a contagious TB patient, positive immunological test for TB infection, suggestive clinical signs and/or a suspicious radiological image.
7. In the absence of microbiological confirmation, anti-TB treatment should be considered according to the degree of radio-clinical suspicion and the potential risk of developing the disease. These cases should be referred to a specialist.
8. A normal or poorly contributing chest XR in an 'at risk' patient clinically suspected of having pulmonary TB needs to be clarified and followed up.

4. Diagnosis of resistance to anti-TB drugs

To tailor treatment to the sensitivity of the strain of *MTBc*, a drug susceptibility test (DST) should always be requested. The laboratory must conduct this test on the first positive culture. It will test first-line drugs, and in case of resistance or in case of an eventual drug-induced toxicity, a sub-culture will be sent to Sciensano to perform testing to 2nd Line TB drugs.

4.1. Drug sensitivity testing to first-line anti-TB drugs

DST to first-line drugs (INH, RMP, EMB and PZA) should be performed on cultures obtained from samples collected before the start of treatment.

A rapid molecular test for RMP resistance should also be performed routinely on the first positive sample (smear and/or PCR positive) regardless of the clinical suspicion of MDR/RR tuberculosis. If the PCR shows R-resistance, the drug susceptibility testing should be enlarged to both first- and second-line anti-TB drugs and therefore a sample (for Xpert® MTB/XDR) and a subculture (for other tests) must be sent to the national reference laboratory¹ or any other laboratory with the necessary equipment and expertise.

High suspicion of MDR/RR-TB

- Proven contact with a patient with MDR/RR-TB.
- Recurrence of active TB previously treated, especially if aggravating factors have been identified (non-compliance during previous treatment, origin from a country with a high prevalence of resistant TB etc.).
- Unsatisfactory clinical, bacteriological and radiological evolution of the patient under treatment.

¹ Sciensano Brussels

A result of in vitro PZA-resistance is not always related with the efficacy of the antibiotic in vivo because of possible false resistance, except for *M. bovis* which is naturally resistant to PZA.

- If a strain is susceptible to PZA, of course one can rely on it.
- If baseline test shows resistance, then we recommend testing for *M. bovis* and/or to perform alternative (e.g. genotypic) testing for PZA-resistance. Awaiting these results, PZA should be maintained in the treatment regimen. In case of a true resistant or *M. bovis* strain, then treatment should be adapted accordingly.

Any diagnosis of multi-drug resistance (resistance to at least INH and RMP) or rifampicin-resistance must be confirmed at the national reference lab by molecular testing and larger antibiotic susceptibility testing (for first- and second-line drugs). In case of discrepant results with the initial laboratory, exogenous contamination of the sample during handling must be ruled out by comparing the genetic fingerprint of strains isolated from several samples. In addition, further tests must be carried out to rule out the presence of antibiotic-resistant non-tuberculous mycobacteria.

If resistance to INH is detected at the standard dose (0.1 µg/mL), the laboratory may perform a resistance test at high dose (0.4 µg/mL). This is particularly important in case a treatment with INH high dose is considered in MDR/RR-TB treatment regimens.

Additional testing for fluoroquinolone susceptibility is indicated in case of intolerance or monoresistance to INH. This is preferably done by (rapid) molecular testing (WGS or Xpert® MTB/XDR) - but can also be done by phenotypic DST - to guide treatment regimen decisions.

In susceptible TB, DST should be repeated in the following cases (31):

- Lack of clinical or radiological improvement, unexpected clinical progression (e.g., patient deterioration), or factors that may promote resistance (such as poor treatment adherence, substance abuse, or malabsorption).
- Reversal from a negative to a positive culture.
- If smear or culture remains positive after 2 months of treatment:
 - In case of positive smear: perform a rapid PCR-based test for RMP-resistance to eliminate the probability of acquired RMP-resistance (of note: PCR is not reimbursed in follow-up, so request reimbursement through BELTA-TBnet).
 - In case of positive culture: send subculture to the national reference lab to perform genetic resistance testing.
 - Phenotypic DST should be repeated, but results will only become available after an additional 6 - 8 weeks.

It is important to note that smear positivity under treatment can sometimes be explained by NTM co-infection. The clinical relevance of the isolated NTM species - and whether treatment is indicated - needs to be evaluated on an individual basis and based on specific DST of the NTM-strain. Another possible explanation for smear positivity under treatment is the presence of non-viable bacteria.

In MDR/RR-TB it is recommended to repeat DST if cultures remain positive by 4 months of treatment and /or unfavourable clinical/radiological evolution under treatment (32).

4.2. Phenotypic drug sensitivity testing to second-line anti-tuberculous drugs

To be requested:

- if the baseline DST confirms:
 - multi-drug resistance (resistance to at least INH and RMP)
 - polyresistance (most frequently resistance to INH and EMB)
 - mono-resistance:
 - > To RMP, usually this will be based on a molecular biology test demonstrating a mutation in the *rpoB* gene
 - > To INH, especially if high level resistance, susceptibility testing for fluoroquinolones should be performed
- in the event of previous treatment
- if culture remains positive after 2 months (or more) of treatment

Phenotypic DST assesses the sensitivity of the strain to second-line antibiotics: amikacin, fluoroquinolones (ofloxacin, moxifloxacin), ethionamid, rifabutin, capreomycin, para-aminosalicylic acid, linezolid, clofazimine, bedaquiline, pretomanid.

4.3. The role of molecular biology techniques

As it takes some time to obtain the results of the phenotypic DST, a molecular test for the rapid detection of resistance to RMP is indicated to detect timely MDR/RR-TB. Molecular detection of resistance to INH may as well be considered, although most RMP-resistant strains are also resistant to INH. This means that, in most cases, molecular confirmation of resistance to RMP, on its own, suggests multidrug-resistant TB.

Of the multidrug-resistant strains isolated in Belgium, 80-100 % have a mutation in the *rpoB* gene and 80-100 % in the *katG* gene and/or in the promotor of the *inhA* gene. Detection of a mutation in these genes confirms that the isolate is resistant to RMP and/or INH respectively, but the absence of a mutation does not mean that the strain is susceptible as other mechanisms of resistance may exist.

Several molecular techniques are available:

- real-time PCR in a cartridge-based system
 - GeneXpert®: can be performed directly on the primary sample. The Xpert® MTB/RIF Ultra cartridge detects *MTBc* and the presence of the main mutations conferring resistance to RMP. The Xpert® MTB/XDR cartridge detects mutations conferring resistance to INH, FQ, SLI, Eto. This test is recommended in case of detection to RMP-resistance. The GeneXpert® MTB/RIF Ultra is the most widely used.
 - Other alternatives are available, some of which detect both RMP and INH-resistance.

- Line Probe Assay: performed on DNA extracted from the clinical sample (preferably if smear is positive) or on DNA extracted from a culture. They can be used to detect the main mutations conferring resistance to first- and second-line antibiotics.
- Whole Genome Sequencing: can be performed on culture. It allows in-depth analysis of the genome and provides:
 - Precise species identification (also identification within the complex)
 - Lineage detection
 - Detailed detection of mutations known to date to confer resistance to first- and second-line antibiotics.

In-depth analyses of the effectiveness of these techniques have been published. They all show a very good correlation between genotypic predictions and the phenotypic susceptibility of *MTBc* to first-line antibiotics. In a large study of 10,000 isolates, resistance to isoniazid, rifampicin, ethambutol and pyrazinamide was correctly predicted with 97.1 %, 97.5 %, 94.6 %, and 91.3 % sensitivity respectively, and susceptibility to these drugs was correctly predicted with 99.0 %, 98.8 %, 93.6 %, and 96.8 % specificity (33).

4.4. Practical issues

4.4.1. What should be done if the DST result is not consistent with the patient's history/clinic?

In that case it is recommended to discuss the case with the microbiology team. DST should be repeated, if possible on a different isolate and/or resistance confirmed by searching for specific gene mutations.

If clinical, microbiological and/or radiological evolution is unfavourable, this may be explained by newly developed resistance, but other factors may be responsible as well: malabsorption, drug-drug interactions, poor treatment adherence, IRIS.

4.4.2. Is it possible for a strain to be only partially resistant to a first-line antibiotic and for the latter to be prescribed?

DST determines whether the proportion of resistant bacilli in an isolate is greater than or equal to 1 % of the total bacterial population. If this is the case, the strain is resistant to the concerning antibiotic. However, the proportion of resistant bacilli can vary from 1 % to 100 %.

Hetero-resistance can be detected by WGS. If the laboratory finds a mix of wild-type with different mutated DNA sequences, it will be reported to the treating physician who may eventually decide to prescribe the concerning antibiotic, especially if there is no (good) alternative.

4.4.3. What should be done if results differ between laboratories?

The national reference laboratory must be notified to investigate the procedure followed by the two involved laboratories (Did they use the same technique? What doses of antibiotics were tested? Did they work on the same isolate? Was sample mislabelled? Problem of specimen mix-up? Co-presence of an NTM? ...). The role of the reference laboratory is also to confirm resistance by repeating the DST and checking for the presence of gene mutations. Genotyping is useful when sample swapping or cross-contamination during sampling or analysis is suspected.

4.4.4. What is the delay for DST results?

First-line phenotypic drug susceptibility testing (performed systematically if culture positive):
on liquid medium: result 2-4 weeks after culture growth.

Second-line phenotypic DST (mandatory if MDR/RR or poly resistance confirmed)
on liquid medium: 2-4 weeks after reception at the national reference lab.

Genotypic DST

GeneXpert: result available within 2 hours once test is started, in practice 24-48h depending on the logistics of the lab

Other PCR techniques: depending on the technique used, to be checked with the lab.

Whole genome sequencing can provide a rapid detection of mutations associated with resistance to both first and second-line drugs. In practice, result is available after 2 weeks.

Line-probe assay tests have a turn-around time of 3 to 10 days.

DIAGNOSIS OF RESISTANCE TO ANTI-TB DRUGS:

Key points

1. Baseline DST must be carried out systematically on the first sample with a positive smear/culture.
2. Every new smear positive result should be subjected to a rapid molecular testing for RMP. If a mutation is detected in the *rpoB* gene, a first- and second-line DST (both genotypic and phenotypic) should be carried out simultaneously by the national reference laboratory.
3. If a smear is still positive after 2 months of treatment, DST should be repeated to check for resistance development. We recommend performing a rapid genotypic resistance testing for RMP in parallel with the classical phenotypic DST to timely detect evolution to MDR/RR-TB. Also, in case of absence of clinical and/or radiological improvement, one can decide to repeat DST on an individual basis.
4. DST for second-line drugs is carried out systematically in the presence of MDR/RR or poly resistance. Rapid molecular tests are available to check for resistance to several second-line drugs.
5. Any DST showing multi-drug resistance must be confirmed by the national reference laboratory.
6. The reliability of DST is limited for certain drugs such as PZA, CS and PAS, which is why doctors may prescribe these antibiotics even though resistance has been diagnosed in vitro.
7. Treatment should not be adapted solely based on DST result. The treating physician should also consider the clinical, bacteriological and radiological evolution.

5. Treatment of drug-sensitive TB

Proper treatment is one of the mainstays of TB control. This chapter describes the therapeutic management of TB without evidence of antibiotic resistance.

5.1. Treatment regimens

5.1.1. Standard treatment

The standard treatment is prescribed in the absence of prior TB treatment and without microbiological arguments for RMP-resistance.

In case of prior TB treatment or in a patient known to have been in contact with an index case with (multi)drug resistant TB, it is highly advised to request rapid larger molecular susceptibility testing (besides the systematic RMP-testing). If possible (depending on clinical context) it can be considered to wait for DST results (genotypic and/or phenotypic), before initiating appropriate treatment.

During the initial phase, four drugs are being prescribed, and two during the continuation phase.

Initial phase: $\text{INH}_7 + \text{RMP}_7 + \text{PZA}_7 + \text{EMB}_7$

Continuation phase: $\text{INH}_7 + \text{RMP}_7$

In subscript: number of days per week that the drug should be taken

EMB is used as protection for unknown possible resistance to INH. Once susceptibility to INH is confirmed, EMB can be discontinued while INH, RMP and PZA are continued until completion of the full two months of the initial phase (34).

The drugs must be taken daily, with the full daily dosage taken at once.

Duration of treatment is generally 6 months (2 months IP and 4 months CP).

- If the IP does not contain PZA (or PZA was stopped prematurely), the CP must be extended to 7 months, so that the total treatment duration is 9 months. The same is true for infections due to *M. bovis* which has an intrinsically reduced PZA-susceptibility.
- A longer treatment time (9-12 months) is recommended in case of severe forms of disease (meningitis, bone TB, miliary or other forms of disseminated TB). In case of CNS-TB, dosing of TB drugs can be increased. For children/adolescents this is discussed in a separate paragraph; for adults dose adaptation is as follows: 10 mg/kg/day (maximum 300 mg per day), PZA 30-40 mg/kg/day (maximum 2 g per day). Ethambutol can be replaced by prothionamide or levofloxacin, those drugs having better brain penetration.

WHO proposes an alternative treatment regimen for some subgroups of pulmonary TB, including a combination therapy of rifapentin, INH, PZA, and moxifloxacin for four months. This regimen is considered equivalent in terms of safety and efficacy, but requires rigorous antimicrobial stewardship since it contains moxifloxacin, a broad-spectrum antibiotic, and a core drug in the treatment of multi-drug-resistant TB (31). Unfortunately, rifapentin is unavailable in Belgium.

5.1.2. General remarks

The first line treatment always consists of a combination of drugs, which varies in the initial phase and continuation phase.

The minimum duration of the initial phase is 2 months.

If a positive sputum smear is found at completion of the intensive phase in pulmonary TB cases treated with an RMP-containing regimen throughout, extension of the intensive phase is not recommended. In that case we recommend performing resistance testing: PCR based on smear, PCR and phenotypic DST on culture-based samples as discussed previously in the chapter on diagnosis of resistance testing. As mentioned before: PCR is not reimbursed by RIZIV/INAMI in context of follow-up ; if the patient is eligible, reimbursement can be provided through BELTA-TBnet.

In case of DS pulmonary TB, even when cavitary disease is present, 90-95 % of patients will have negative sputum cultures after 3 months of treatment containing RMP and INH. The majority also show clinical improvement. In the event of delayed (clinical and/or microbiological) treatment response, careful evaluation (e.g. adherence, resistance, malabsorption, drug interactions, diabetes, concurrent malignancy etc.) is warranted.

The treatment must be adapted according to DST results, which will generally be available by month 2. Check DST results prior to switching from initial to continuation phase of TB therapy.

If the DST results of the index case (source of infection) are known, these must be considered in order to assess the probability of infection by a resistant strain.

Medical history must always be assessed. Patients treated previously for TB are at higher risk for (multidrug-)resistant TB. If the treating physician is not/less familiar with management of TB, it is advisable to refer the patient to an expert physician.

The same treatment regimens are generally prescribed for both pulmonary and extrapulmonary TB.

TB meningitis and other forms of CNS-TB have a poor prognosis. Hence it is wise to have a low threshold to initiate TB treatment for possible TB meningitis/CNS-TB. Especially young children and others with poor immunity against *MTBc*, like PLHIV, are at increased risk for TB meningitis and prompt initiation of treatment has a significant impact on disease outcome. Presumptive treatment can always be stopped later, once TB diagnosis is discarded. Starting treatment too late is more harmful than starting therapy that, in retrospect, proved unnecessary.

Broadly speaking, the same principles of treatment apply to children, pregnant women, breast-feeding women and PLHIV. In the latter case, adjustments are sometimes necessary if antiretroviral drugs are also prescribed at the same time (see section on PLHIV).

Treatment failure is defined as the absence of culture conversion by month 5. Possible reasons should be promptly addressed, and samples should be sent for susceptibility testing to first- and second-line drugs. Consult an expert physician if not familiar with treatment failure.

A single new drug is **never** to be added to a failing regimen as it can lead to amplification of drug resistance!

5.1.3. Treatment in case of TB relapse

Patients who have been classified 'cured' or 'treatment completed' after a previous treatment and who show signs of TB relapse should be retreated. Most relapses occur within 6-12 months following treatment completion. It is impossible to distinguish a relapse from a new infection (with a different strain) without genotyping the strains isolated at the time of the first and second episode of active TB.

Consider referring the patient to a physician with expertise in retreatment cases, as an adjustment of the initial treatment with second-line drugs may be required.

Awaiting the DST result, the treatment is prescribed depending on the probability of drug resistance. This can never be completely ruled out, especially if information on prior treatment is not available or unreliable.

5.1.4. Treatment adaptation in case of unfavourable evolution

Unfavourable evolution = worsening of clinical signs, and/or extension of the radiological lesions, and/or continuous or recurrent positivity of the direct microscopic examination and culture. If sputum monitoring shows positive direct microscopic examination but negative culture, this should not be considered an unfavourable evolution as positive smears without positive culture can be explained by presence of residual non-viable bacilli.

Refer the patient to a specialist, especially if it concerns a case of TB relapse.

In case of unfavourable evolution:

- Check treatment compliance, which can also be affected by the occurrence of side effects.
- Assess possibility of intestinal malabsorption, drug interactions or lab error.
- Rule out a co-infection with another potential pathogenic micro-organism.
- Consider alternative co-existing diagnosis as e.g. malignancy.
- Exclude HIV and/or a paradoxical reaction, which is more frequent in case of TB/HIV co-infection but can also occur during treatment of any TB case, especially in case of lymph node TB, disseminated or neurological forms of TB.
- Rule out drug resistance based on DST. If the result indicates drug resistance, refer to a specialist in management of resistant TB. If it concerns a strain that was susceptible at the time of diagnosis: check whether any acquired (multi-)resistance has occurred during treatment, based on a rapid molecular test to detect RMP resistance (not reimbursed by RIZIV/INAMI in context of follow-up ; if the patient is eligible, reimbursement can be provided through BELTA-TBnet). If a mutation in the *rpoB* gene is present, new extended DST (for first- and second-line drugs) should be performed and patient should be referred to a specialist in management of MDR/RR-TB.

- **Never** add a single antibiotic to a failing drug regimen. Consult specialists before making any treatment regimens changes that go beyond standard first-line therapy to prevent further resistance from developing.

5.1.5. Management in case of adherence problems or treatment interruption of limited duration

In case of treatment adherence concerns, it is advisable to refer the patient to a specialist. The following strategy is recommended:

- Systematically perform clinical, radiological and bacteriological assessment.
- Identify, analyse and tackle the possible reasons for adherence problems.
- Supervise drug intake, if necessary with the help of the Respiratoire Gezondheid (VRGT)/FARES nurses
- Adjust the treatment schedule according to these results:
 - In case of an unfavourable evolution: see above
 - In case of a favourable evolution: see [table 5](#). This approach considers the duration and timing of the treatment interruption (35).

Table 5: Approach in case of irregular intake of first line drugs, in a patient with favourable evolution

Timing of interruption	Duration of interruption	Approach	
Initial phase	< 2 weeks	Prolong initial phase until all originally foreseen doses are taken	
	≥ 2 weeks	Restart treatment from the beginning of the initial phase	
Continuation phase	< 4 weeks	Microbiology negative baseline	Further treatment may not be necessary
		Microbiology positive baseline	Prolong treatment until all originally foreseen doses are taken
	> 4 weeks	If treatment was taken regularly and cumulative lapse < 3 months	Prolong treatment until all originally foreseen doses are taken, unless the duration of interruption is > 2 months
		Lapse is ≥ 3 months in duration.	Restart full treatment (both IP and CP) after new work-up.

5.1.6. Dosage and administration

Drug dosing considers age and weight as described in [table 6](#). Daily dosing is standard; intermittent use is no longer recommended.

In cases of severe TB (meningitis, miliary TB ...) there might be a need to increase dosage in the initial phase of the treatment.

In the presence of renal insufficiency, EMB and PZA should be prescribed three times a week at the daily regimen dosage. If the patient undergoes dialysis, the anti-TB treatment should be administered after the session.

Table 6: Dosing of first-line drugs for treatment of drug-susceptible TB

Drugs	Daily Administration (mg/kg)		Daily maximum dose
	Children	Adults	
Isoniazid (INH)	10-15 (12-15)*	5 (10)*	300 mg (400 mg in children/ adolescents in CNS-TB)*
Rifampicin (RMP)	15-20*	10*	600 mg*
Pyrazinamide (PZA)	30-40**	25 (30-40)*	2000 mg
Ethambutol (EMB)	15-25	15 (25)*	1600 mg
* in certain situations, the dose may be increased - to discuss with expert ** body weight: 25kg or more: aim the lower dose range Pyridoxine dosing discussed in paragraph on additional drugs (see below)			

Ideally, the daily dose of each TB drug should be taken in one administration. In presence of gastro-intestinal problems, the dose of PZA can be divided into two.

The pharmacokinetics of INH and RMP are substantially affected by food intake, hence these drugs should be taken during a fasting state, i.e. one hour before or two hours after food intake, preferably with water (or apple sauce for infants).

Phototoxicity: all first-line TB drugs (except for RMP) have photosensitising capacity (36). Therefore, it is advisable to inform patients with tuberculosis before starting treatment and suggest using sun protection while they are taking these medications.

FARES/Respiratoire Gezondheid (VRGT) can provide supervision and support for all TB patients to ensure completion of the full course of therapy. Directly observed therapy (DOT) is recommended for patients with poor adherence. This to limit the risk of developing resistance.

5.1.7. Monitoring during treatment

Table 7 gives an overview of the minimal monitoring to be provided when treating a person with (pulmonary) TB. This can be adjusted according to the individual needs depending on the specific patient situation.

Table 7: General approach in monitoring TB-patients										
	diagnosis	D15	M1	M2	M3	M4	M5	M6	M9	M12
Clinical review	x	x	x	x	x	x	x	x	(x)	x
Sputum smear microscopy	x	x		x			x			
Mycobacterial culture	x			x			x			
Drug susceptibility testing	x			Repeat if unfavourable clinical evolution and/or persistent positive smear/culture at 2 months of treatment						
Chest XR*	x			x				x	(x)	(x)
Liver function tests	x		x	x						
Coagulation test	x									
Renal function	x									
Complete blood count	x			(x)						
C-reactive protein	(x)									
HIV-serology**	x									
Hepatitis serology**	(x)									
Visual acuity/colour discrimination	x	Actively inquire at each encounter in patients taking EMB								
* Only indicated in case of pulmonary TB; in specific cases such as miliary or mediastinal lymph node TB chest CT may be preferable										
** After consent of patient, results to be managed in a confidential way										

Clinical review is recommended monthly, either by the general practitioner or the treating physician, and includes a review of symptoms and questioning for possible treatment side-effects, adherence issues, as well as physical exam, including body weight. In case of significant body weight increase, check weight-based dosing of drugs and adapt accordingly.

Blood tests requested at diagnosis/start of therapy serve as a baseline and reference for future results. Monitoring can be guided by clinical presentation/evolution. Given the potential hepatotoxicity, liver function tests need to be checked monthly during the initial phase. In patients at risk for drug-induced hepatitis (pregnancy, women in postpartum, elderly, alcohol users, PLHIV ...) liver function tests may require monitoring even thereafter, or when clinically indicated.

Additional hepatitis B and C serology testing is recommended in persons at increased risk for hepatotoxicity, such as PLHIV, people from African and Asian descent, IV drug users.

At month 2, review initial DST results, which should be available by then and adjust therapy in case of resistance, preferably after consultation of a TB expert.

Repeat sputum smear microscopy and culture at month 2 at the latest. If spontaneous sputum production is no longer possible on treatment, one can try expectoration following sputum induction with hypertonic saline solution in a well-ventilated room.

We advise against the use of PCR test on sputum in the routine follow-up of TB treatment. PCR tests can remain positive for a long time (up to several years) after treatment completion/cure without clinical relevance nor implications.

Repeating DST is not required beyond diagnosis unless following circumstances:

- unfavourable evolution and acquired drug resistance is suspected
- positive smear and culture after 2 months of treatment:
 - In case of positive smear: perform a rapid PCR-based test for RMP-resistance (of note: PCR is not reimbursed in follow-up, request reimbursement through BELTA-TBnet)
 - In case of positive culture: send subculture to the national reference lab to perform PCR for resistance testing
 - Phenotypic DST should be repeated with results available by month 3 or 4 of treatment.
- Reversion to positive after having converted

In case of unfavourable or delayed treatment response, consult an expert.

Follow-up beyond treatment completion may be indicated for patients at higher risk of relapse on a 6-monthly basis up to 2 years.

5.1.8. Most common drug–drug interactions

Physicians initiating TB treatment should ascertain that concomitant medication do not interact with TB drugs. Some interactions of note:

- Antacids should not be taken within two hours of TB drug intake because they can reduce the absorption of INH, RMP and EMB. Depending on the indication, discontinuation is recommended.
- Isoniazid is an inhibitor of cytochrome P450, especially CYP2C9, CYP2C19 and CYP2E, which can increase plasma levels of anticonvulsants (phenytoin, carbamazepine, valproic acid); benzodiazepines (diazepam, triazolam), oral anticoagulants and disulfiram.
- Rifampicin is a potent inducer of cytochrome P450 (CYP3A and CYP2C), which can lead to increased metabolism (hence, decreased blood levels) of numerous drugs including oral contraceptives, warfarin and some other anticoagulants as DOACs, sulfonylureas, and methadone (**Table 8**). Caution is indicated in HIV-infected patients being treated with protease inhibitors (PIs) and most non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Pyrazinamide decreases serum concentrations of cyclosporin and antagonises the effects of probenecid.

Publicly available drug interaction checkers are: <https://reference.medscape.com/drug-interactionchecker>; https://www.drugs.com/drug_interactions.html; or on subscription: https://www.upToDate.com/drug-interactions/?source=responsive_home#di-druglist

Table 8: Common drug-drug interactions with anti-TB drugs

Drug class	Molecules with substantial decrease in concentration	Possible action
Antiretrovirals		
	See section on HIV	
Antimicrobials		
	Macrolide	Clarithromycin and RFB result in bidirectional changes in drug levels. Erythromycin is a CYP3A4 substrate (sub-therapeutic level) of rifamycins. No significant interaction between azithromycin and RMP, hence priority to use azithromycin in case a macrolide is prescribed.
	Anti-fungal agents	Itraconazole, ketoconazole and voriconazole levels may be sub-therapeutic with any rifamycin. Drug monitoring is recommended.
	Atovaquone, chloramphenicol, mefloquine	Consider alternate agent
Hormone therapy		
	Oestrogen therapy	Women of childbearing potential should be advised to use additional barrier contraceptive when on a rifamycin.
	Levothyroxine	Monitor thyroid hormone levels and adapt substitution if needed
Narcotics		
	Methadone	Use of rifamycins may require methadone dose increase
Anticoagulants		
	Warfarin	Monitor INR and adapt warfarin dosing if needed
Immunosuppressive agents		
	Cyclosporin, tacrolimus	Preferably use RFB; monitor serum concentrations of immunosuppressive agents to assist dosing
	Corticosteroids	Steroid dose increase (2-3x) may be required; monitor clinically
Anticonvulsants		
	Ethosuximide, Lamotrigine, Phenobarbital ...	Check with treating neurologist, TDM if available
Cardiovascular agents		
	Calcium channel blockers, beta-blockers, ACE-I	Consider change to alternate drug; monitor clinically
	Anti-arrhythmic	TDM recommended or change to alternate drug
Antidiabetics		
	Sulfonylurea	Monitor blood glucose; dose increase may be required or change to alternate drug
Hypolipemics		
	Simvastatin, fluvastatin	Monitor lipidaemia; dose increase may be required or change to alternate drug
Psychotropic drugs		
		Monitor clinically; dose increase may be required or change to alternate drug

5.1.9. Side effects: monitoring and management (37)

Orange coloration of secretions such as urine, faeces, sperm and tears (which can cause coloration of soft lenses) is caused by RMP and this should be mentioned prior to treatment initiation. Increased uric acid blood levels may be associated with PZA intake. Both phenomena can be an indicator of good treatment adherence.

A transient rise in liver function tests is common in the first few weeks of TB treatment and does not necessarily require drugs discontinuation unless transaminases rise > 3x upper limit of normal (ULN) in the presence of symptoms or >5x ULN (regardless of symptoms) or in case of significant bilirubin elevation (> 3 mg/dL or even lower) and/or jaundice. True hepatotoxicity risk is higher with PZA (especially high dosage) than INH or RMP. PZA-related hepatotoxicity generally appears later. Severe hepatotoxicity may develop at any stage of treatment. Patients should be advised to seek medical attention promptly if they experience symptoms such as abdominal pain or loss of appetite.

Table 9: First-line drugs for treatment of drug-susceptible TB and most important side effects and their management

Drug	Adverse reactions	Monitoring and possible action
Isoniazid		
	Hepatotoxicity	Perform liver function tests & clinical monitoring. Usually baseline liver tests are performed and controlled 1-2 times during the first month of treatment. If tests are normal and there are no clinical signs of liver toxicity, further testing during treatment is unnecessary. If transaminases rise >3xULN and symptoms are present or >5xULN (regardless of symptoms) or significant bilirubin elevation and/or jaundice: stop all TB drugs. Wait for liver function to recover (TA <2xULN); re-initiate consecutively the different drugs at <u>full dose</u> . Restart RMP with EMB, then consecutively reintroduce INH and later PZA. Goal is to re-establish the full regimen in 10 days while checking liver function tests every 3-5 days. If INH cannot be given, then consider using a quinolone providing strain is susceptible. In case liver toxicity recurs after rechallenging with PZA while tolerating well INH and RMP or acceptable liver function alterations persist under treatment with INH-RMP (± EMB) or the toxicity event was very severe; treatment with PZA can be omitted definitively while prolongating the full treatment duration to 9 months
	Peripheral neuropathy	Clinical monitoring and appropriate management of neuropathy if development of symptoms. Add pyridoxine as prophylaxis in patients at increased risk of neuropathy (HIV, diabetes, malnutrition, alcohol abuse, pregnancy ...).
	CNS toxicity: memory loss, psychosis, seizures	Exclude other explanations, consider stopping the drug
	Fever and skin rashes	Clinical monitoring. Consider (temporarily) discontinuing drug
Rifamycins (both rifampicin and rifabutine)		
	Hepatotoxicity	Cfr. supra
	Hypersensitivity reaction	Clinical monitoring. Consider discontinuing drug if severe and/or associated symptoms.
	Cytopenia	Complete blood count: baseline check and control if suspicion of toxicity
	Gastro-intestinal disorders	Exclude underlying liver toxicity. Adjusting timing of drugs may be helpful. Provide symptomatic treatment if indicated.
	Orange discolouration of secretions	Inform patient

Table 9: First-line drugs for treatment of drug-susceptible TB and most important side effects and their management

Drug	Adverse reactions	Monitoring and possible action
Rifabutin		
	Uveitis	Clinical monitoring. Refer to ophthalmologist.
Pyrazinamide		
	Hepatotoxicity	Cfr. supra
	Hyperuricaemia with/without subsequent arthritis	Clinical monitoring. If symptomatic: consider giving NSAID or increasing anti-gout drugs.
	Skin rash	Clinical monitoring.
	Gastro-intestinal disorders	Exclude underlying liver toxicity. Adapting timing of drugs may be helpful, daily PZA dose can be divided in 2. Provide symptomatic treatment if indicated.
Ethambutol		
	Ocular toxicity	Visual acuity and colour discrimination during routine follow-up, referral to ophthalmology if abnormal findings. Immediate discontinuation of the drug; do not re-introduce. Symptoms resolve usually if promptly stopped.

5.1.10. Treatment of special populations

1) Treatment of children with TB

TB disease is more often paucibacillary. Therefore, in some cases a short course of treatment can be proposed. Shorter duration can increase treatment compliance and completion. If a child between 3 months and 16 years of age fulfils the criteria for non-severe drug-susceptible TB disease, a shorter course of treatment can be proposed (38).

1. Treatment of non-severe drug-susceptible TB in children

A non-severe TB disease is either a peripheral lymph node TB, or an intra-thoracic lymph node TB without airway obstruction, or uncomplicated pleural effusion, or paucibacillary pulmonary TB confined to one lobe without cavities and without miliary pattern.

This shorter treatment is prescribed if

- the patient fulfils the criteria for a non-severe disease (cfr. supra)
- there is no suspicion of or proven MDR/RR-TB
- if no history of prior TB treatment in the last two years
- the child has > 3 months and < 16 years of age

Drugs must be taken daily in this short duration treatment.

Initial phase (2 months): INH₇ + RMP₇ + PZA₇ + EMB₇

Continuation phase (2 months): INH₇ + RMP₇

In subscript: number of days per week that the drug should be taken

If DST becomes available and shows a full susceptible strain, EMB can be stopped prior to the completion of the initial phase.

Children with severe acute malnutrition must be treated with a 6-month duration regimen.

Children with peripheral lymph nodes TB disease can experience a seemingly delayed clinical response to TB treatment. This is frequently seen in children where lymph nodes can remain enlarged even after treatment. Nevertheless, it is important to evaluate the possibility of treatment failure.

For adolescents aged 12 years and above, an alternative and shorter treatment regimen including a combination therapy of rifapentin, INH, PZA, and moxifloxacin for 4 months is possible. However, as stated earlier, rifapentin is currently unavailable in Belgium. This regimen is considered equivalent in terms of safety and efficacy, but requires rigorous antimicrobial stewardship since it contains moxifloxacin, a broad-spectrum antibiotic, moreover with an important place in the treatment of multi-drug-resistant TB.

2. Standard treatment of drug-susceptible TB in children

This treatment is prescribed to

- children who do not fulfil the eligibility criteria for a four-month treatment
- children living with HIV fulfilling the non-severe criteria but being immunocompromised
- CNS-TB cannot benefit from this regimen (see below)

As for adults, during the initial phase four drugs and during the continuation phase two drugs are recommended. Drugs must be taken daily.

Initial phase (2 months): INH₇ + RMP₇ + PZA₇ + EMB₇

Continuation phase (4 months): INH₇ + RMP₇

In subscript: number of days per week that the drug should be taken

If DST becomes available and shows a full susceptible strain, EMB can be stopped prior to the completion of the initial phase.

Duration of treatment of pulmonary TB should be prolonged to 9 months in case of cavities and/ or if culture of sputum is still positive after 2 months treatment.

3. Treatment of CNS-TB and osteo-articular TB in children

Patients < 16 years of age with bacteriologically confirmed or clinically diagnosed CNS-TB or osteo-articular TB should be treated for a total duration of 12 months. Children diagnosed with CNS-TB should be referred to a physician with expertise in this domain. It is important to state that miliary TB is often associated with CNS-TB, hence there should be a low threshold to treat miliary TB as a CNS-TB (39).

In case of CNS-TB: an IP including a four-drug regimen (HRZE) should be prescribed for 2 months and a CP with a two-drug regimen (HR) for 10 months. INH can be used at higher dose: 12-15 mg/kg/day with a maximum of 400 mg daily. Dosage of PZA in this setting is 30-40 mg/kg/day with a maximum of 2 g per day. Because ethambutol does not pass the blood-brain barrier well, it can be replaced by prothionamide (15-20 mg/kg/day with a maximum of 1 g/day) or by levofloxacin at a dose of 16-20 mg/kg/day up to a maximum of 750 mg daily (or 1 g for children/adolescents above 45 kg). Once DST shows susceptibility to the first line drugs (INH, RMP, PZA), prothionamide or levofloxacin can be stopped.

In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.

4. Treatment of neonates with TB disease

Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the six-month treatment regimen. At diagnosis, congenital tuberculosis should be ruled out, referral to a paediatric TB specialist is warranted. Treatment may require dose adjustment to reconcile the effect of age, quick weight gain and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in the management of paediatric TB.

5. Adverse events in children

Side effects of TB treatment are less common in children compared to the adult population (40). Nevertheless, monitoring of side effects can be more challenging in children.

- In the youngest TB-patients, it is difficult to ensure ophthalmological follow-up. Nevertheless, it is warranted to ensure ophthalmological follow-up in any child receiving ethambutol given the severe long-term effects if toxicity develops and is not properly managed.
- Hepatotoxicity of isoniazid in children is rare but may occur and can exceptionally be lethal. In young children, it is recommended to maintain a low threshold for performing liver function tests, as their ability to accurately report abdominal symptoms may be limited. TB patients and their parents should be informed of the risks and benefits of treatment and encouraged to seek prompt medical advice (ideally within 24h) in the event of anorexia, nausea, jaundice or vomiting. If such symptoms occur, serum transaminase and bilirubin levels should be checked.

2) Treatment during pregnancy and lactation

Pregnant women with pulmonary drug-sensitive TB may be treated as other adults suffering from drug sensitive TB disease. The risk of developing complications and/or drug toxicity is however higher in pregnant and postpartum women. Therefore, a referral to a specialist might be considered.

In the past the use of pyrazinamide was controversial in this setting, however actual recommendations are in favour of using pyrazinamide during pregnancy and lactation.

Pregnant women have a potential increased risk of isoniazid-induced hepatitis, and liver function should be monitored closely.

Vitamin K supplementation is already recommended for all infants at birth. Attention should be increased for children born to a mother who received TB-treatment during pregnancy. Special focus on correctly administered vitamin K supplementation to these newborns is required to reduce the risk of haemolytic anaemia following exposure to rifampicin via the placenta.

It is recommended to contact a paediatric TB specialist prior to childbirth so a plan for treatment and work-up of the newborn can be prepared in advance.

3) Treatment of patients with pre-existing liver disease

To assess the likelihood of drug-induced hepatitis (and differentiate from pre-existing liver disease) perform baseline transaminase tests in all patients, and hepatitis B and C screening in patients with a history of IV drug use or originating from an hepatitis virus endemic regions, or with HIV infection. Tuberculous hepatitis can also cause elevated transaminases which will improve with TB treatment.

The crucial activity of RMP and INH warrants their use, if possible, even in the face of pre-existing liver disease. Close monitoring by a specialist and clear instructions are to be provided. Certain symptoms such as jaundice, anorexia, nausea, vomiting or abdominal discomfort necessitate consultation with a physician without delay. In case of jaundice, all drugs must be stopped immediately.

In case of severe hepatic insufficiency and/or deterioration of biological liver tests during standard TB therapy, alternative treatment regimens can be considered (41) (42). Initiation of these alternative regimens and follow-up of these patients should be done in consultation with an expert in management of complex TB.

In case of development of significant drug-induced liver toxicity by TB-drugs, treatment will be interrupted with stepwise reintroduction of TB-drugs after liver function test returned to < 2x ULN, starting with EMB, RMP, INH and eventually PZA (see also [table 9](#)). In most cases, full RHEZ regimen can be introduced; sometimes not. In that case, alternative regimens can be considered.

- No PZA: INH₇ + RMP₇ + EMB₇ (2 months) followed by INH₇ + RMP₇ (7 months)
- No INH: RMP₇ + EMB₇ + PZA₇ (6-9 months) or RMP₇ + EMB₇ + PZA₇ + FQ₇ (6 months) throughout provided DST for FQ has shown FQ-susceptibility
- No INH and PZA: RMP₇ + EMB₇ + FQ₇ (12-18 months) provided DST for second-line drugs is performed
- No RMP and PZA: treat as RR-TB (see chapter MDR/RR-TB)
- Full liver sparing: EMB₇ + FQ₇ + SLI (18-24 months). This approach is sometimes applied temporarily when severe liver toxicity occurs. However, it is often possible to switch to an RMP-based regimen later, which can significantly shorten the overall treatment duration. A separate regimen is applied for children: EMB₇ + FQ₇ + LZD₇/DLM₇/CS₇ (9-18 months).

In subscript: number of days per week that the drug should be taken, dosing of SLI can vary (daily, 5 times a week or 3 times a week in case of prolonged use).

If these schedules are not suitable, we recommend seeking expert advice.

During these alternative treatment regimens, it is important to regularly monitor liver function tests as well as clinical, radiological and bacteriological evolution to confirm effectiveness of the therapy. Initiation of these alternative regimens and follow-up of these patients should be done in concertation with an expert in management of complex TB.

4) Treatment of people living with HIV (PLHIV) (43)

All TB patients must have HIV serology done at diagnosis because of the management implications of TB-HIV co-infection.

Treatment of PLHIV must consider the potential drug-drug interactions with the antiretroviral treatment, the risk of the immune reconstitution inflammatory syndrome and therefore the optimal timing for initiation of ART.

Recommendations for TB treatment in PLHIV are like those in HIV-negative adults. The standard of care consists of daily administration of standard TB therapy with an initial phase of a four-drug regimen for 2 months followed by a continuation phase of a two-drug regimen for 4 months. The initiation of ART must be made with close attention to the timing of initiation with TB medications.

1. TB diagnosed prior to HIV diagnosis

Initiation of TB treatment must start as soon as possible but TB treatment and ART should not be started simultaneously (44).

The ART should be started within 2 weeks after initiating anti-TB therapy, this regardless of CD4 count, especially if CD4+ cell count < 50 cells/mm³.

For patients with suspected or confirmed CNS-TB, ART should be delayed for the first 4 weeks of anti-tuberculous therapy, except in case of CD4+ cell count < 50 cells/mm³ (8 weeks).

Considering the risk of IRIS in persons starting early ART at low CD4+ count levels: administration of prednisone for 4 weeks at the time of ART initiation (prednisone 40 mg qd for 14 days, then 20 mg qd for 14 days) in PLHIV with CD4+ < 100 cells/mm³ starting ART within 30 days of starting TB-treatment could decrease the risk of IRIS (45).

2. TB diagnosed in patients with previously known HIV diagnosis and receiving antiretroviral therapy

PLHIV already on ART should be offered TB treatment as soon as possible and should not interrupt their ART.

The potential DDIs must be checked and a switch of treatment applied if some are significant. See [table 10](#) for a more detailed overview.

Drug-drug interactions and choice of ART:

- TDF/FTC + DTG is recommended as first-line ART for people taking rifampicin-based TB treatment. TDF/FTC/EFV can be used as an alternative (if DTG not available or not tolerated)
- Some adjustment of the TB medications may be also necessary depending on the ART regimen chosen.
 - RMP is not recommended in people receiving PIs, DOR, ETR, NVP, FTR and is then replaced by RFB.
 - BIC, EVG/c, CAB/RPV LA, COBI, RPV should not be co-administered with RMP or RFB.
- For more details: see Liverpool interaction checker <https://www.hiv-druginteractions.org/> or European Aids Clinics Society website <https://eacs.sanfordguide.com/drug-drug-interactions-other-prescribing-issues/drug-drug-interactions/anti-tuberculosis-drugs-arvs>

Table 10: Recommended dosing for TB drugs according to ART

TB drug	ART drug	Daily dose of TB drug
Isoniazid		
	All ART	5 mg/kg, maximum 300 mg
Rifampicin – Note: DTG*, RAL*, and MVC* doses need to be adjusted when used with rifampicin.		
	HIV PIs, DOR, ETR, NVP, RPV, FTR, BIC, CAB, CAB/RPV LA, EVG/c.	Not recommended
	TAF	Use with caution
	All other ART	10 mg/kg, maximum 600 mg
Rifabutin – Note: DOR** and RPV doses** need to be adjusted when used with rifabutin.		
	PI with COBI, TAF, RPV (IM), BIC, CAB (IM), EVG/c-containing regimens	Not recommended
	DTG, RAL, DOR, EFV, or RPV (po only***)	5 mg/kg, maximum 300 mg
	HIV PIs with RTV	150 mg daily
	EFV	450 mg
Pyrazinamide		
	All ART	Weight-based dosing • Weighing 40–55 kg: 1000 mg • Weighing 56–75 kg: 1500 mg • Weighing ≥76 kg: 2000 mg
Ethambutol		
	All ART	Weight-based dosing • Weighing 40–55 kg: 800 mg • Weighing 56–75 kg: 1200 mg • Weighing ≥76 kg: 1600 mg
Adapted from https://eacs.sanfordguide.com/ois/diagnosis-treatment-of-tuberculosis , https://www.bhiva.org/file/5c485f3dc7c17/BHIVA-TB-guidelines.pdf and https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/tuberculosis-hiv-coinfection . * DTG: 50 mg bid when given with rifampicin, RAL: 400 or 800 mg bid, MVC: 600 mg bid ** DOR: 100 mg bid, RPV: 50 mg qd when co-administered with rifabutin. *** IM Long-acting RPV is not recommended with rifabutin. po RPV can be used but the dose should be increased to 50 mg daily, international guidelines (US, BHIVA, EMA, EACS) vary on the use of RPV, in most cases there're enough alternative ART-options to combine with rifamycins. po DOR dose adjustment: 100 mg bid		

5.1.11. Approach to radiological abnormalities found in adults suspect of (prior) TB without microbiological confirmation of TB.

Not all TB cases will have microbiological proof of active TB. Nevertheless, absence of microbiological proof does not exclude this diagnosis.

Radiographic findings (with or without clinical signs) suggestive of TB are a common situation, for instance in the context of TB-screening with a positive tuberculin skin test. Some radiographic signs are suggestive of healed prior TB (calcified solitary pulmonary nodules, calcified hilar lymph nodes, pleural thickening) without an increased risk of reactivation. These patients can receive TBI treatment according to the same principles for people with TBI-diagnosis and normal radiographic findings, unless they received treatment for active disease in the past.

If chest XR shows other signs of (prior) TB (mainly fibronodular apical scarring, often with volume loss) the risk of reactivation of TB is increased (16). These radiological findings may be compatible with active TB, hence a full microbiological work-up is warranted. If no microbiological proof of TB is found, an alternative diagnosis should be excluded (especially in symptomatic patients). If the diagnostic work-up does not reveal an alternative diagnosis and microbiology is negative, 2 different approaches are recommended.

- In patients with clinical presentation compatible with TB and no evidence of prior treatment for TB, a standard regimen may be started. In some cases, final culture results will be positive, these patients will hence follow the classical treatment approach for active TB. If final culture results is negative, treatment continuation will be decided based on the clinical and radiological evaluation at 2 months: if treatment response (either clinically or radiographically or both) is established, treatment will continue for active TB. According to some studies the continuation phase in this setting can be shortened to 2 months of INH and RMP (46).
- In asymptomatic patients, one may wait until the final culture results (available after 6-8 weeks). At that time a new chest XR may be performed to check for radiographic evolution. In case of positive culture and/or radiographic deterioration, treatment for active TB will be initiated. In case of negative culture and stable radiographic findings, decision to start treatment will depend on the patient's situation. If the risk of reactivation is deemed significant, such as in younger patients where radiographic evidence of tuberculosis can be attributed to a recent or semi-recent infection, or in immunocompromised patients, treatment is generally advised in most instances. In this setting a TBI-regimen is recommended, with priority given to a combination of INH-RMP for 3 months, which is a safer option given the lower risk of induced resistance if the patient was incorrectly classified and has culture-negative, active TB-disease (47). In patients where reactivation risk is considered low and risk of adverse effects of preventive treatment outweighs the reactivation risk, a simple follow-up is justified.

It's noteworthy to mention that the approach is different in children, where in case of any findings suggestive of TB, the threshold to initiate treatment is very low.

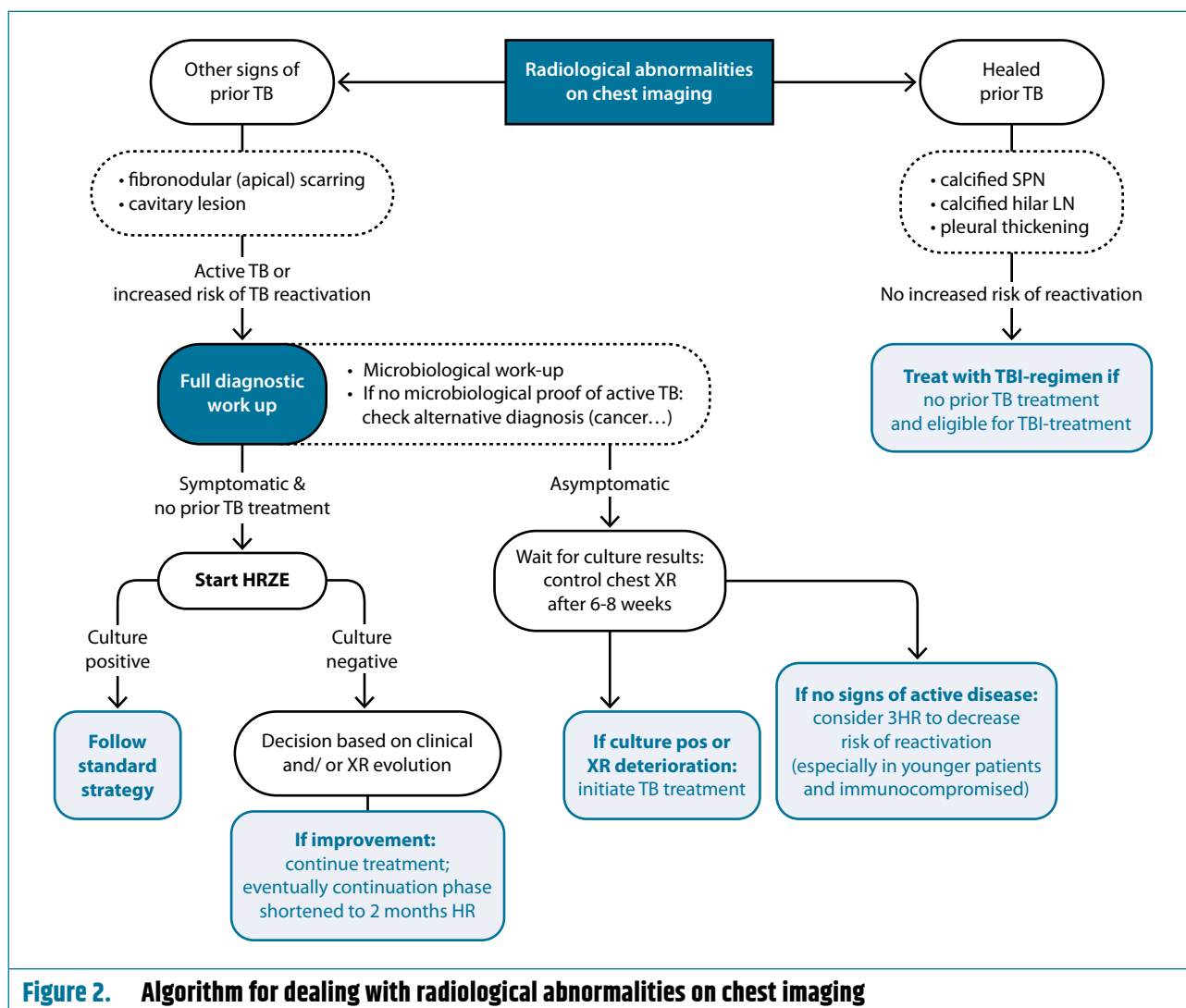


Figure 2. Algorithm for dealing with radiological abnormalities on chest imaging

5.2. Additional drugs

5.2.1. Pyridoxine (Vitamin B6)

Patients at risk for development of peripheral polyneuropathy through vitamin B6 depletion caused by isoniazid should receive supplemental pyridoxine. These risk groups are patients with diabetes, malnutrition, vegan diet, infants that are exclusively breastfed, pregnancy, alcohol abuse etc (48).

Use of pyridoxine in patients without these risk factors is not recommended given free circulating pyridoxine (due to high intake) may induce, in turn, polyneuropathy (49).

The usually recommended dosage in prevention is 10 mg daily (except for young children < 5 kg: 5 mg daily) (50). The dosage usually prescribed in Belgium is 100 or 250 mg per week (due to the commercially available formulations in pharmacy). In children dosage is 1-2 mg/kg/day with a

maximum of 50 mg per day, especially if exclusively breastfed, vegan diet, malnutrition or HIV infection. Since oral tablets of pyridoxine mono are no longer available in Belgium, usually Befact Forte® (which includes 250 mg of pyridoxine (Vit B6) along with other vitamins is now used (for adults 1 tablet per week; for children 1-12 years old 0,5 tablet per week and children < 1 year old 0,25 tablet per week). Other options are magistral preparation, Vitamine B6 Sterop® and TriBVit®.

5.2.2. Corticosteroids

In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used since it decreases the risk of fatal outcome, severe disability and disease relapse (31). There is a (theoretical) advantage of dexamethasone over prednisolone because of the better CNS penetration. The recommended doses are as follows (51):

- Adults: dexamethasone 0.4 mg/kg/d 1st week, 0.3 mg/kg/d 2nd week, 0.2 mg/kg/d 3rd week, 0.1 mg/kg/d 4th week, then tapered to stop over 3-4 weeks
- Children: IV dexamethasone 0.3-0.4 mg/kg/d or oral prednisolone 2-4 mg/kg/d (max 60 mg/day) for 4 weeks then tapered to stop over 4 weeks.

For HIV-positive adults with TB-meningitis, adjuvant corticosteroid therapy does not appear to be beneficial, but in the absence of an effective alternative, corticoids are still recommended on a case-by-case basis according to EACS-guidelines. Also, in children with HIV and TB-meningitis it is likely not advantageous either (52).

In patients with TB pericarditis, initial corticosteroid therapy should not be used routinely. It may be used to prevent the development of constrictive pericarditis in patients at high risk (high levels of inflammatory markers, large amount of pericardial fluid, early signs of constrictive pericarditis), although the evidence is less convincing, particularly in the case of HIV-co infection (53).

As mentioned above, corticosteroids are recommended in prevention of IRIS in certain situations. They will also be used in the management of severe IRIS.

They are also indicated in the presence of mediastinal lymph nodes causing compression with a reduction in bronchial diameter of more than 50 %. In children with miliary TB use of corticosteroids should be evaluated on a case by case.

In other forms of active TB, initial adjuvant corticosteroid therapy should not be considered.

5.2.3. Acetylsalicylic acid

Through addition of acetylsalicylic acid in adults with tuberculous meningitis, less brain infarcts and improved survival was reported in patients taking acetylsalicylic acid and dexamethasone compared with placebo and dexamethasone, especially at a high acetylsalicylic acid dose. It is recommended to obtain an MRI to look for evidence of ischaemia or infarction. If there are no infarctions, acetylsalicylic acid may be started because this may lower mortality and reduce the risk of stroke (51, 54, 55).

TREATMENT OF DRUG-SUSCEPTIBLE TB:

Key points

1. Drug Administration and Dosage:
 - Standard treatment uses isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB), with dosing adjusted by age and weight.
 - Daily administration in single dose is advised; RMP and INH preferably on an empty stomach, for better absorption. Adjustments may be required for severe cases and specific populations, such as those with renal insufficiency.
2. TB drugs can interact with various medications, especially antacids, anticonvulsants, and antiretrovirals. Monitoring is crucial to manage potential reductions in drug efficacy.
3. Common side effects include hepatotoxicity, cytopenia and photosensitivity. Liver function tests, complete blood count, and regular clinical assessments are part of routine monitoring.
4. The typical duration is 6 months. However, severe cases (e.g., CNS-TB) may require prolonged treatment.
5. Special Populations:
 - Children, pregnant women, people with liver issues, and those with HIV require tailored TB management to mitigate specific risks.
 - Children with non-severe TB can sometimes receive a shortened four-month course.
6. Regular follow-up is essential to track adverse events and treatment efficacy, with sputum tests recommended to confirm bacterial eradication. Adherence support, such as directly observed therapy, is advised for patients at risk of non-compliance.
7. In cases of relapse or treatment failure, adjustments to drug regimens may be necessary. It's recommended to consult TB specialists for advice.
8. Additional drugs:
 - Pyridoxine (= vitamin B6) is advised to prevent neuropathy from INH in high-risk patients for peripheral neuropathy
 - Corticosteroids and aspirin may benefit cases involving TB meningitis.

6. MDR/RR-TB management

6.1. Causes of resistance

Multiple mechanisms of resistance development have been described.

Different intrinsic mechanisms can be responsible for evolution to resistance. A non-exhaustive list of these mechanisms include: impermeability lipid membrane, efflux pumps and mutations leading to modifications of the antibiotic target.

Extrinsic mechanisms are caused by human errors such as inappropriate prescription of TB drugs, lack of effective drugs, ineffective combination of TB drugs, and non-adherence to prescribed treatment. Another extrinsic cause is inappropriate bio-disponibility of prescribed drugs caused by individual variability, malabsorption and drug-drug interactions.

6.1.1. Risk factors for MDR/RR-TB

Most MDR/RR-TB is transmitted and not acquired. However, the diagnosis of resistance may have been missed when the patient was diagnosed the first time. Rifampicin-based treatment is not effective when resistance to rifampicin, the most important first-line drug, is present. Therefore, previous TB diagnosis and unsuccessful rifampicin-based treatment are the main risk factors of having MDR/RR-TB (56).

Systematic review analysis identifies several other risk factors:

- history of non-completion and failure of TB treatment
- poor treatment response (e.g. lack of conversion, persisting TB symptoms, ...)
- high bacillary burden, thus higher risk for a spontaneous mutation to occur
- non-adherence to treatment (risk factors: adverse drug reactions, male gender, unemployment, lack of health insurance, homelessness, history of imprisonment)
- patients ≥ 40 years of age
- HIV infection

Risk factors not mentioned in the systematic review but typically linked to a higher risk for resistant TB are provenance from a country with a high burden of MDR/RR-TB and being a contact of a person diagnosed with MDR/RR-TB. Yearly WHO reports list the high burden countries (57).

6.1.2. Experienced Management

MDR/RR-TB is a complex disease to be treated. Designing an optimal treatment regimen requires more than combining a number of likely active TB drugs. Management by an experienced team is recommended to guarantee an optimal approach to this disease by integrating specific medical recommendations while providing psychosocial support to reach the most optimal treatment outcome.

6.2. Definitions

6.2.1. RR/MDR/XDR-TB (58)

- RR-TB: strain resistant to at least RMP
- MDR-TB: strain resistant to both INH and RMP
- Pre-XDR TB: strain that fulfils the definition of MDR/RR-TB with also resistance to any fluoroquinolone
- XDR-TB: strain that fulfils the definition of MDR/RR-TB while also resistant to any fluoroquinolone and at least one additional Group A drug (BDQ or LZD)

6.2.2. Outcome of treatment (59), (60)

WHO published new outcome definitions in 2021. These definitions are listed below:

- Treatment failure: permanent regimen change or termination due to no response to treatment (bacteriologically or clinically), an adverse drug reaction or amplification of drug resistance.
- Cure: completion of treatment as recommended by the national policy with evidence of bacteriological response and no evidence of failure in a case of pulmonary TB with bacteriologically confirmed TB at the beginning of treatment.
- Completion: completion of treatment as recommended by the national policy and the outcome does not meet the definition for cure or treatment failure.
- Death: death of patient for any reason before starting treatment or during treatment.
- Loss to follow-up: no treatment started in a TB-patient or treatment interruption for 2 consecutive months or more.
- No evaluation: patient for whom no treatment outcome was assigned. This category includes patients transferred out to another treatment centre or country but for whom no feedback on treatment outcome was obtained. This category excludes patients defined as ‘loss to follow-up’.
- Treatment success: sum of cured and treatment completed as defined above.

Programs are usually not equipped to monitor recurrence after cure or treatment completion. Patients are monitored after the end of treatment only in studies. Sustained treatment success

or relapse-free cure is then usually defined as being alive and free of TB when assessed at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment. Recurrence can be either relapse or a re-infection. Relapse is the occurrence of a new episode of TB disease, with the same strain involved in the previous episode. Re-infection is the occurrence of a new episode of TB disease, with a strain different from the one involved in the previous episode. The distinction between relapse and re-infection is only possible when genotypic data are available for both the baseline and recurrence strain.

6.3. Diagnosis

This item is discussed in details in the chapter 4. Diagnosis of resistance to anti-TB drugs.

It's important to emphasise the role of rapid resistance testing for every new TB-diagnosis by using most optimal techniques (POCT PCR). If a new resistant strain is diagnosed, rapid FQ-resistance testing should be performed (Xpert® MTB/XDR, SL LPA ...).

6.4. Treatment Regimen

6.4.1. Before full DST

Guidance

The chance of achieving a successful treatment outcome depends on the combination of TB drugs in the regimen. The regimen should include at least one core drug. We use the term core drug for TB drugs with both high bactericidal and sterilising activity. High and early bactericidal activity is required to rapidly reduce the bacillary load, to reduce TB symptoms, increase the chance of survival and reduce the risk of resistance acquisition and treatment failure. Sterilising activity is required to also kill semi-dormant bacilli and to prevent relapse (new episode of TB after cure or treatment completion because of insufficient elimination of TB bacilli). Known core drugs are rifampicin, the cornerstone of first-line treatment, later generation fluoroquinolone (such as moxifloxacin and levofloxacin), and bedaquiline. Fluoroquinolone and bedaquiline are used in the treatment regimen when resistance to rifampicin is diagnosed. Pretomanid, a relatively new drug, may be another core drug. Other drugs add bactericidal activity and/or sterilising activity.

Treatment for MDR/RR-TB has changed a lot in the past decade. Not so long ago all patients with MDR/RR-TB were treated for 18 months or longer, while success was achieved in not much more than 50 %. Such long regimens have now become an exception. New shorter treatment regimens are available for most forms of resistant TB, with better results (treatment success of 80 % or higher). Every year results from different trials are published. International guidelines are therefore updated on a yearly basis. This implies that this document will also require regular updates.

How to decide which regimen should be started? Ideally a clinician knows which core drugs are still effective. In practice, the clinician needs to wait several weeks for the full DST results. Therefore, before starting treatment, rapid DST results must be performed to show whether the

patient has TB susceptible or resistant to rifampicin. In case RR-TB is detected, another rapid test must be performed to detect a resistance to fluoroquinolone (and/or isoniazid). Rapid DST for bedaquiline is not available.

In case DST shows susceptibility to a core drug, although the patient has previously been treated unsuccessfully with a regimen containing this core drug, this drug can be included in the regimen but should not be considered as a core drug because resistance might have been missed on DST. For MDR/RR-TB susceptible to fluoroquinolone on rapid DST, a short MDR/RR-TB treatment regimen can be started.

For MDR/RR-TB resistant to fluoroquinolone on rapid DST (pre-XDR TB), or in case of any other contraindication for the short MDR/RR-TB treatment regimen, a short pre-XDR TB treatment regimen can be started.

For MDR/RR-TB resistant to both fluoroquinolone and bedaquiline, or previously unsuccessfully treated with a regimen containing these drugs, or in case of contraindications for the use of the short pre-XDR TB treatment regimen, a long individualised regimen will be required, based on a full DST result.

In general, it is important to think in terms of regimen and not on individual drugs. Indeed, if a resistance to one drug is reported during an ongoing treatment (full DST is usually available when treatment has already started) or if one drug is discarded because of side effect, it is bad practice to change only this one drug for another one. As well, in case a regimen is not effective (ongoing bacillary multiplication during treatment), adding one drug may result in acquired resistance to the added drug.

In exceptional cases, one could decide to wait before starting treatment. But this should be discussed with the Belgian MDR expert group. The decision to not start at time of diagnosis is when a patient is paucisymptomatic and has been heavily pretreated (especially if FQ and BDQ were used), provided they are non-infectious or that adequate isolation is organised while awaiting DST results.

6.4.2. Based on full DST

1) Short regimens

Different studies using shorter standardised regimens in MDR/RR-TB patients in several countries showed excellent results (61), (62).

As from May 2016, a standardised short regimen was recommended by WHO for MDR/RR-TB patients (63). These first short regimen included a second-line injectable (SLI) in the initial phase of the treatment. Following encouraging data from national programs, there was a shift to an all-oral short regimen with bedaquiline replacing the SLI since December 2019 and endorsed by WHO (64). Later on, a RCT showed that all-oral short regimens were superior compared to the SLI-containing short regimen (65).

Meanwhile, multiple trials have shown that 6-month regimens work, if they combine pretomanid with bedaquiline and linezolid (BPaL). A first study, the Nix-TB trial (66), assessed this option (including high-dose linezolid, at 1200 mg/day) for patients with highly drug-resistant TB, mainly pre-XDR TB. A cure rate of 90 % was achieved. However, high-dose linezolid was associated with too many adverse events.

Subsequent trials showed that similar good outcomes can be obtained with the same combination, but with 600 mg of linezolid (ZeNix trial) (67). If used for fluoroquinolone-susceptible MDR/RR-TB, moxifloxacin can be added (BPalm), as in the Practecal trial (68), which confirmed good outcomes for BPalm-based regimens. In that trial, linezolid 600 mg daily for 16 weeks was used, then 300 mg daily for 8 weeks. BPalm instead of BPalm was used in case of baseline resistance to fluoroquinolone. WHO now recommends 600 mg of linezolid throughout, with the option to reduce the dose to 300 mg in case of toxicity. If culture is still positive between months 4-6 or clinical condition is suggestive for progressive TB, treatment can be extended to 9 months (32). In case of treatment interruption of more than 7 days, treatment duration can be extended under following criteria: the corresponding doses of a 26w or 39w regimen should be taken in a period of maximum 7 or 10 months respectively to make up for missed doses.

This evidence has led to the recommendation to prioritise the BPalm or BPalm (the latter in case of FQ-resistance or contraindication to FQ) regimens in most patients with diagnosis of MDR/RR-TB or pre-XDR TB.

Patientss, regardless of HIV status, can be treated with this 6-month all-oral regimens if:

- They suffer from pulmonary or extrapulmonary TB, except for disseminated (miliary) or osteo-articular forms or TB with CNS involvement
- They are 14 years or older
- They are not pregnant or breastfeeding (data on use of this regimen in this setting are very scarce)
- There was no previous exposure $\geq$ 1 month to BDQ, LZD, Pa or DLM, unless resistance to these specific drugs have been ruled out.

Special attention is needed for eventual drug-drug interactions. For instance, in PLHIV, the preferred ART regimen is dolutegravir-based and 2 nucleoside reverse transcriptase inhibitors. Drugs with significant QTc-prolonging effect are contraindicated as well as CYP3A4-inducers and -inhibitors and MAO-inhibitors.

More recently WHO recommended 2 other short standardised regimens (69).

The following 6-month regimen, based on the BEAT-TB trial (70), showed excellent results in both MDR/RR and pre-XDR TB patients, including in specific populations such as children, adolescents and pregnant/breastfeeding women. This regimen consisting of bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (spelled out as 6BDQ-DLM-LZD-Lfx-CFZ) can be started regardless of DST-results for fluoroquinolone once MDR/RR-TB is confirmed. If the final DST-results show resistance to fluoroquinolones, levofloxacin should be dropped. In case of susceptibility to fluoroquinolones, clofazimine can be dropped. If no result on fluoroquinolone susceptibility is obtained, both levofloxacin and clofazimine should be continued throughout the regimen.

Another treatment option is a strategy based on the END-TB trial where 5 different 9-month regimens were compared (71). This strategy is of particular interest in patients with severe disease and co-morbidities (HIV, DM, Hepatitis B/C) or in pregnant/breastfeeding women. This strategy is not applicable in case of fluoroquinolone-resistance, neither in case of previous exposure to bedaquiline, delamanid and/or linezolid. Different 9-month regimens can be used: either bedaquiline, linezolid, moxifloxacin and pyrazinamide.(BLMZ), or bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide (BLLfxCZ) or bedaquiline, delamanid, linezolid, levofloxacin, pyrazinamid (BDLLfxZ). Priority is given to BLMZ as this strategy contains only 4 drugs. In case linezolid and/or bedaquiline cannot be used, then a 9-month treatment with the

combination of delamanid, moxifloxacin, clofazimine and pyrazinamide (DMCZ) is an option. In children, the BDLLfxZ regimen is not recommended according to the Sentinel guidelines (72).

An alternative option is another 9-month all-oral regimen in cases not eligible for the BPALM/BPaL, BEAT-TB or end-TB regimens. This regimen consists of bedaquiline (used for 6 months), in combination with 4 months of levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine, followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. Ethionamide can be replaced by 2 months of linezolid (600 mg daily). It is spelled out as 6BDQ-9Lfx(Mfx)-4Eto-4Hh-9E-9CFZ-9Z or 6BDQ-9Lfx(Mfx)-2LZD-4Hh-9E-9CFZ-9Z (with a 2-month extension of all drugs except BDQ if the patient remains sputum smear positive at the end of month 4).

Patients, regardless of HIV status, can be treated with this 9-month all-oral regimen if:

- There is no proof of resistance to fluoroquinolone (hence the importance of doing rapid DST)
- There is no proof of extensive TB disease or severe extrapulmonary TB
- There was no or less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid or clofazimine (in case of previous exposure, DST results will determine whether the regimen is still recommendable, or if it needs to be adapted)

The endTB-Q trial is a study evaluating exclusively patients with pre-XDR (73). A regimen with bedaquiline, clofazimine, delamanid and linezolid (BCDL) showed good treatment outcome results in patients without severe forms of TB. Treatment duration is 6 months, but in case of delayed treatment response, it is expanded to 9 months. This regimen has not been recommended in international guidelines yet.

The most used regimens are BPAL(M) and BEAT-TB, the alternative regimens can be used if there is a contraindication for these 2 regimens. An overview of the different regimens and their criteria to use or contraindication is listed in **table 11**.

Table 11: Overview of different standardized MDR/RR-TB regimens

REGIMEN	USED DRUGS	DURATION	CRITERIA
BPAL(M)*	Bedaquiline, pretomanid, linezolid ± moxifloxacin	6 months (24 weeks)	• ≥ 14 years • can be used in PLHIV • duration can be prolonged to 9 if culture positive between 4-6 months or on clinical indication • not in disseminated TB, no osteo-articular TB, no CNS-TB • not in pregnant/breastfeeding women • not in case of previous exposure to BDQ, LZD, Pa or DLM, unless resistance is ruled out
BEAT-TB*	Bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC)	6 months	• can be used in children, pregnant/breastfeeding women • levofloxacin dropped if confirmed FQ-R, clofazimine dropped if confirmed FQ-S • not in case of previous exposure to BDQ, DLM or LZD

Table 11: Overview of different standardized MDR/RR-TB regimens

REGIMEN	USED DRUGS	DURATION	CRITERIA
endTB*	• BLMZ (bedaquiline, linezolid, moxifloxacin, pyrazinamide) • BLLfxCZ (bedaquiline, linezolid, levofloxacin, clofazimine, pyrazinamide) • BDLLfxZ (bedaquiline, delamanid, linezolid, levofloxacin, pyrazinamide) • DMCZ (delamanid, moxifloxacin, clofazimine, pyrazinamide)	9 months	• can be used in extensive forms of TB • preferred regimen: BLMZ; DMCZ-regimen to be used only if BDQ and/or LZD is not an option • In children: prioritize BLMZ or BLLfxCZ • linezolid dose reduced to 300mg qd in case of adverse effects or after 4 months of treatment • not in pregnant/breastfeeding women • not to be used in case of fluoroquinolone-resistance • not in case of previous exposure to BDQ, DLM or LZD
endTB-Q	BCDL (bedaquiline, clofazimine, delamanid and linezolid)	6-9 months	• in patients with pre-XDR TB • 9-month duration in case of delayed clinical/ bacteriologic response to therapy • Not in extensive TB disease or severe extrapulmonary disease
9m all oral WHO 2022*	6BDQ-9Lfx(Mfx)-4Eto-4Hh-9E-9CFZ-9Z 6BDQ-9Lfx(Mfx)-2LZD-4Hh-9E-9CFZ-9Z	9 months	• can be used in PLHIV • all 7 drugs are not given throughout: ethionamide and high dose isoniazid are used for 4 months and bedaquiline used for 6 months; if ethionamide is replaced by linezolid, the latter should be used for 2 months • extension of all drugs except bedaquiline if patient is still smear positive at the end of 4 months. • Not in case of fluoroquinolone-resistance • Not in extensive TB disease or severe extrapulmonary disease • not in case of previous exposure to bedaquiline, fluoroquinolones, ethionamide/linezolid or clofazimine, unless it was < 1 month

* Regimens recommended by WHO to date

2) Individualised longer regimen

Longer individualised regimens (usually 18-20 months of treatment) have been used for many years in management of MDR/RR-TB, but nowadays the indications to use those regimen are rare, except in cases with XDR-TB or in case of contraindication/intolerance to an appropriate short standardised regimen.

In case an individualised regimen has been started before obtaining the full drug susceptibility results, the treatment regimen should be reevaluated for its effectiveness once full DST results are available, in order not to expose the patient to ineffective drugs or to a too extensive (in length and/or number of drugs) treatment.

How do we construct an active regimen for patients not eligible for the above-described short treatment regimens?

Lessons learnt from decades of research on first-line and second-line treatment regimens show that it takes more than adding a few ‘likely active’ drugs to construct a regimen. Ideally each regimen has a core drug to rely on. The problem is that many patients not eligible for standardised short regimens may have a TB strain resistant to all core drugs and/or may have been exposed to all core drugs. As the most powerful drug exerts most selection pressure, resistance develops first to the most powerful drug of the regimen used. Therefore, one must always assume resistance to a core drug which has been used in a previous unsuccessful treatment, especially if bacillary replication continued during the ongoing treatment and treatment failure was finally declared. Resistance is less frequent in patients with relapses, as relapse may be a sign of a too short treatment duration. Even if drug susceptibility testing shows susceptibility to a core drug previously used, resistance may still be present, e.g. in the form of hetero-resistance, with only a subgroup of bacteria being resistant.

In the absence of a likely effective core drug, a salvage regimen will need to be built, preferably guided by phenotypic and genotypic DST results. Decisions will be made based on low-level evidence. Ideally, the activity of drugs included in the regimen will complement each other, to assure bactericidal and sterilising activity.

The following guidance can be used to build up a (salvage) regimen (74).

Previously used core drugs may be reused at a high dosage, to overcome any low-level resistance. Drugs known as with core drug activity are rifampicin, later generation fluoroquinolone, and bedaquiline. Fluoroquinolone, preferably levofloxacin, may be recycled, and prescribed at a very high dose (1500 mg for 55–64 kg, 1750 mg for ≥ 65 kg). For bedaquiline at high dose, only anecdotal evidence is available.

- Pretomanid may be another core drug. However, as for now, we do not recommend its use in an individualised salvage regimen, but only in the context of a BPAL(M)-regimen.
- Drugs known to add high and early bactericidal activity are isoniazid (to be used at high-dose for MDR/RR-TB), the second-line injectable drug amikacin (in the all-oral era they may not have been used in previous regimens and can play an important role in salvage regimens) and meropenem with amoxicillin-clavulanate (administration requires hospitalisation or home nursing). Other drugs that add bactericidal activity are ethionamide (or prothionamide), linezolid and delamanid.
- Sterilising activity can be obtained, adding clofazimine and pyrazinamide.
- Considering the lack of core drug activity, the doubtful effect of previously used drugs, and the probability that some of the drugs may need to be interrupted due to adverse events, it is recommended to include at least 5 drugs.
- The principle of prioritizing Group A agents in MDR/RR-TB patients on longer regimens remains, but the possibilities will be limited, as these longer regimens “salvage treatment” are initiated in a context of resistance to one or more of these agents. The target is to start treatment with at least four TB agents likely to be effective. In case bedaquiline is included, then a minimum of three other agents must be included, to be continued for the rest of treatment, after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

Table 12: Drugs used in MDR/RR-TB

Drug	WHO group	(Main) mechanism of action	Bactericidal / Bacteriostatic	Standard dosing	Dosing in children	Practical aspects**
Amikacin	C	Binds to mycobacterial ribosome leading to inhibition of translation	Bactericidal	15 mg/kg qd 5-7 times/week; lower to 2-3 times/week after culture conversion	15-20 mg/kg qd	• IV access needed • Aim for peak concentration of 35-45 µg/mL
Bedaquiline	A	Inhibition mycobacterial ATP synthase	Bacteriostatic & Bactericidal	400 mg qd during first 14 days, 200 mg 3 times/week for 22 weeks	6 mg/kg qd first 14days, 3-4 mg/kg 3 times/week for 22 weeks	• To be taken with food • Agreement needed from national MDR-TB Expert Group
Clofazimine	B	Prodrug reduced by NADH dehydrogenase releasing reactive oxygen	Bacteriostatic	100 mg qd	2-5 mg/kg qd	• To be taken with food • To be ordered abroad • Agreement needed from national MDR-TB Expert Group
Cycloserine	B	Inhibition of mycobacterial cell wall synthesis	Bactericidal ± Bacteriostatic	10 to 15 mg/kg; maximum daily dose 1000 mg (usually 750 mg)	15-20 mg/kg qd	• dose ramping (250 mg qd 3 days, 250 mg bid 3 days followed by 250 mg morning-500 mg evening) • To be taken on empty stomach
Delamanid	C	Inhibition of mycobacterial cell wall synthesis and cell respiration	Bactericidal ± Bacteriostatic	100 mg bid for 24 weeks	3-4 mg/kg/d in bid dosing	• To be taken with food • To be ordered abroad • Agreement needed from national MDR-TB Expert Group
Ethambutol	C	Inhibition of mycobacterial cell wall synthesis	Bacteriostatic	15-25 mg/kg qd; 25 mg/kg only used during first 2 months	15-25 mg/kg qd	To be taken with or without food
Fluoroquinolone	A	Inhibition mycobacterial DNA gyrase	Bacteriostatic & Bactericidal	Levofloxacin: 750-1000 mg qd moxifloxacin: 400 mg qd	Levofloxacin: 15-20 mg/kg qd moxifloxacin: 10-15 mg/kg qd	• To be taken with food • 2h before/after this drug: – No dairy products – No antacids – No divalent cations (Fe, Mg, Ca, Zn) or vitamins • Sun protection recommended
High dose Isoniazid	*	Inhibition of mycobacterial cell wall lipid synthesis, depletion of nucleic acid pools and metabolic depression	Bactericidal	10-15 mg/kg qd	15-20 mg/kg qd	• To be taken 30' prior to meal and at least 120' after last meal • No antacid medication 60' before/after INH

Table 12: Drugs used in MDR/RR-TB

Drug	WHO group	(Main) mechanism of action	Bactericidal / Bacteriostatic	Standard dosing	Dosing in children	Practical aspects**
Linezolid	A	Inhibition mycobacterial ribosome leading to inhibition of translation	Bactericidal	600 mg qd	15 mg/kg qd <16 kg; 10-12 mg/kg qd ≥ 16 kg	- To be taken with or without food - Avoid excessive exposure to tyramine (aged cheese, red wine, soy sauce ...)
Meropenem	C	Inhibition of mycobacterial cell wall synthesis	Bactericidal	2000 mg tid (usually decreased to bid if outpatient management)	20-40 mg/kg tid	- Amoxicillin/clavulanic acid (125mg) to be used as companion agent, 30-60' prior to MPM administration, ideally just before eating to increase tolerability - IV-access needed
PAS	C	Inhibition synthesis of mycobacterial DNA precursors	Bacteriostatic	4000 mg bid or tid	200-300 mg/kg in bid dosing	- Dose ramping (increase every 3-4 days with 4000 mg) recommended to increase tolerability - To be stored in fridge - Best tolerated if mixed with yoghurt, apple sauce
Prothionamide/ Ethionamide	C	Inhibition of mycobacterial cell wall synthesis	Bacteriostatic	15-20 mg/kg/day, usually bid dosing; maximum daily dose 1000 mg	15-20 mg/kg/d, usually bid dosing	- Dose ramping (increase every 3-4 days with 250 mg) recommended to increase tolerability - To be taken with food
Pyrazinamide	C	Exact mechanism unclear	Bacteriostatic	25-40 mg/kg qd; maximum dose 2000 mg	30-35 mg/kg qd	- To be taken with or without food - Sun protection recommended
Drugs not recommended in individualised regimen						
Pretomanid	*	Inhibition of mycobacterial cell wall synthesis	Bactericidal ± Bacteriostatic	200 mg qd for 26 weeks		- To be taken with food - To be ordered abroad - Agreement needed from national MDR-TB Expert Group

* not mentioned in WHO-classification of second-line drugs

** Monitoring and management of adverse events mentioned later in this guideline

Duration of longer individualised regimens

A total treatment duration of 18-20 months (15-17 months after culture conversion) is suggested for most patients in this setting. The duration may be modified depending on the treatment response and/or tolerance. The use of amikacin in longer regimens is usually limited to an intensive phase of maximum 6-7 months.

6.4.3. The specific situation of MDR/RR CNS TB

When selecting drugs for a treatment regimen of MDR/RR-TB of the central nervous system, it is important to consider the penetration of the respective drugs in the central nervous system.

Drugs penetrating the CNS well:

- levofloxacin and moxifloxacin
- prothionamide (or ethionamide, but not available in Belgium)
- cycloserine (and terizidone, but not available in Belgium)
- linezolid
- meropenem
- high dose isoniazid and pyrazinamide

Second-line injectables (e.g. amikacin) penetrate CNS only in the presence of meningeal inflammation.

All these drugs with (reasonable) CNS penetration should be used at doses as high as possible. In that regard TDM might be useful to ensure effective but safe blood concentrations.

Ethambutol does not penetrate the CNS well and should not be counted as an effective agent for MDR/RR CNS-TB. Likewise for p-aminosalicylic acid, although this might be better in the presence of meningeal inflammation.

Small studies suggest good bedaquiline penetration into the CSF, but others do not.

There are also limited human data for delamanid and pretomanid but there appears to be a good brain tissue penetration (better than CSF) in animal models.

There is little data on CNS penetration of clofazimine.

6.5. Surgery in pulmonary MDR/RR-TB (75)

In selected patients, a surgical approach may be needed as part of the treatment. Decision to proceed to surgery should preferably be discussed in the national MDR-TB Expert Group and performed in experienced centres, not only to have an optimal surgical outcome but also to ensure optimal peri-operative management regarding isolation measures, TB-treatment etc.

Determining the indications for surgery presents challenges and is currently grounded primarily in expert consensus. Prerequisites are at least that the infecting strain shows an extensive drug resistance with a high likelihood of treatment failure or relapse. The TB-lesion should also be limited and resectable (using a maximal parenchymal-sparing technique and considering functional preoperative evaluation of the patient) and adequate postoperative treatment should be possible to enable control of remaining mycobacterial infection and allow bronchial stump healing.

6.6. Treatment failure

Building an optimal regimen never guarantees treatment success. To prevent treatment failure, it is important to recognize risk factors of treatment failure.

Some risk factors are related to poor treatment adherence. Interventions targeting an optimal treatment adherence can consist of the following measures: social interventions (e.g. housing for homeless people), optimise nutrition (e.g. access to social grocery store and/or restaurants, meal vouchers ...), management of language barriers (e.g. providing translator during (medical) visits), enable correct treatment intake by providing pill boxes. A close collaboration with Respiratoire Gezondheid (VRGT) and/or FARES will help to facilitate these aspects.

As MDR/RR-TB is a rare disease and requires experience in clinical management, optimal communication with other caregivers is key to avoid treatment modifications made by caregivers not experienced in TB-management.

Other risk factors for treatment failure are unrelated to treatment adherence. For example, adverse events (AE) might require treatment modifications, eventually to a less robust regimen. Other examples are drug-drug interactions or malabsorption (the latter especially in patients with comorbidities such as IBD, HIV, diabetes). Optimal management of these last risk factors can be guided through therapeutic drug monitoring (TDM). Regarding AE-management, TDM can guide us to find the optimal drug dosage (still maintaining effectiveness but avoiding AE). In case of malabsorption, drug dosages higher than the standard can be given if TDM shows suboptimal bio-disponibility. Similarly for drug-drug interactions: optimal drug dosage (higher or lower than standard) can be monitored through TDM.

In Belgium TDM for TB drugs is performed in the lab LHUB-ULB. Contact the lab prior to sending samples to ensure optimal handling. For contact details: see chapter on practical aspects.

6.7. Follow-up

6.7.1. Medical

Medical follow-up for DR patients is not that different from the non-DR ones. Close monitoring is easily organised in hospitalised setting. For the follow-up during the ambulatory phase, a medical check-up visit should be planned at least monthly. If for some reason, it is decided to follow the patient on an outpatient basis from the beginning of treatment, it is advisable to see the patient on a weekly basis, given important side effects usually occur from the start.

TB patients will be asked for symptoms suggestive of disease activity and checked for possible drug-related toxicities. A multidisciplinary approach is advisable (nurse, social assistant, medical doctor).

Taking various medications daily, that can potentially cause many adverse effects as well as the fear of treatment failure, has an enormous impact on the patient's physical and mental well-being. Therefore, close collaboration with a psychologist is advisable for many patients.

Measuring body weight is a standard parameter in follow-up. Other clinical parameters depend on the patient's situation.

6.7.2. Technical Exams

1) Medical imaging

- Targeted imaging (mostly chest XR) should be performed at baseline, at 2 months of effective treatment, at the end of treatment and at the end of the post treatment follow-up phase.
- Supplementary imaging should be performed in case of treatment failure suspicion (clinical deterioration, poor treatment adherence ...).
- More detailed imaging by chest CT is justifiable at the end of treatment, mainly to have an optimal comparator scan in case of suspicion of relapse. Prior to discussion of eventual surgical treatment, it is also required to perform CT imaging.
- In case of extra-pulmonary disease, choice of imaging will depend on disease localisation. Interval and indication of imaging are similar for pulmonary TB.
- Use of FDG-PET/CT in clinical management of TB can be useful in some cases (some types of extra pulmonary TB, identification of subclinical TB ...), although guidelines in these settings are not (yet) established. In the specific situation of resistant TB, use of PET/CT is rarely indicated but can be useful to assess treatment response. Nevertheless, FDG-uptake does not necessarily correlate with active infection and might be the signature of residual inflammation without infection present. Decision to use PET/CT should be taken after multidisciplinary discussion to avoid overuse of a costly and possible harmful (radiation exposure) procedure (76).

2) Microbiology

In pulmonary TB, sputum monitoring throughout the treatment is recommended. More invasive procedures (induced sputum or bronchoscopy) in case the patient is unable to give any sputum, can be performed in suspected treatment failure or relapse.

In extrapulmonary TB, samples are to be taken only in case of suspicion of treatment failure or relapse.

Guidance on interval of sputum monitoring:

- Initially, during the hospitalization phase, a weekly smear & culture test is recommended. This will enable a closer look at sputum conversion but will also facilitate decisions on isolation measures (see chapter 'Epidemiology and Public Health considerations for TB prevention').
- During the ambulatory phase of follow-up, monthly monitoring of sputum is recommended (if the patient still can provide sputum).
- PCR testing is not recommended as treatment monitoring. Presence of residual DNA of dead bacilli may result in a positive PCR test and may still be present even years after TB-disease without any arguments for TB recurrence.

Sputum conversion is defined as 2 sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. The date of the first set of negative cultures and smears is used as the date of conversion.

3) Lab monitoring

Biological tests performed during the follow-up should be planned according to the baseline abnormal findings that need follow-up, a standardised toxicity monitoring depending of the used drugs (see [table 13](#) on treatment monitoring) and other tests on specific indications.

Baseline tests should be performed in all patients before treatment initiation: kidney function, thyroid gland function, whole blood cell count, glycaemia, liver function, albumin. Also screening for HBV, HCV, HIV is mandatory. Vitamin D measurement is recommended as Vitamin D plays an important role in immunity control and substitution is recommended in case of deficiency. Additional tests will be done on an individual basis.

4) Technical procedures

When performing specific procedures like endoscopy, surgery, sputum induction: adapted personal protective equipment & adequate ventilation in the procedure room are required. This is also discussed in the chapter 'Epidemiology and Public Health considerations for TB prevention'.

5) ECG

Several TB-drugs and ancillary drugs for side-effects management can have QTc-prolonging effects. ECG monitoring should be performed baseline and on a weekly basis during the first month of treatment in case these drugs are used. Afterwards a monthly ECG control during treatment is advisable (77).

If QTc-prolongation is diagnosed, it is best to seek cardiologist's advice before stopping all QTc-prolonging medication. The pros and cons should be carefully weighed as some TB medications and combinations can be lifesaving and there is often no alternative.

6) Audiometry

In case SLI are used, baseline and monitoring audiometry is recommended. Systematic check for audiovestibular symptoms is mandatory during each follow-up visit. If you have any doubt, refer for audiometry.

7) Ophthalmologic exam

Clinical monthly monitoring (ideally including Snellen & Ishihara test) should be performed when ethambutol, linezolid and/or clofazimine are used. If the test or the symptoms suggest toxicity, refer to ophthalmology. It is legitimate to perform a baseline ophthalmologic test in older patients as they might already experience visual impairments due to pre-existing comorbidities. If deterioration under therapy should happen, baseline test results will help to determine whether the used TB-treatment is the cause.

6.7.3. Treatment plan (Annexe 1)

The treatment of an MDR/RR-TB patient can take a very long time (20 to 24 months, sometimes) and so can the follow-up (even 24-48 months). Several practitioners are involved and it is not obvious that one practitioner will follow the entire process. It is very important to work out a treatment plan from the start, in which the resistance pattern (genotypic and phenotypic) can be traced, the core medication and additional medication can be indicated, the duration of treatment can be found, some clinical data can be noted and investigations can be planned. This document can be consulted by any practitioner during the treatment and can be given to the patient so that he/she becomes involved in his/her treatment. A link to the template form can be found in the chapter on practical aspects.

6.8. Causes and management of side effects

In MDR/RR-TB regimens, a lot of adverse events can occur. In these regimens it is not always clear to determine which drug is responsible.

Adverse effects of first-line drugs were already discussed in the chapter on drug-susceptible TB. **Table 13** gives an overview of the second-line drugs, their possible adverse effects, the proposed routine monitoring and the eventual management of adverse effects.

As with drug-susceptible TB, it is advisable to check for drug-drug interactions using one of the available online interaction checkers.

Table 13: Most important side effects of second-line drugs for MDR/RR-TB treatment and their management

DRUG	ADVERSE REACTIONS	MONITORING	MANAGEMENT
Amikacin			
	Renal toxicity	Baseline and monthly kidney function	Dose reduction to administration 3 times a week, stop treatment if needed
	Electrolyte imbalance (HypoK, HypoMg)	Baseline and monthly electrolytes	Electrolyte supplementation if needed
	Otovestibular toxicity	Baseline audiometry, eventual monthly monitoring. Baseline peak & trough levels	Referral to ENT-specialist if symptoms
	Cutaneous hypersensitivity		Ancillary medication if needed, topical treatment. Stop medication if severe reaction.
Amoxicillin/clavulanic acid			
	Gastro-intestinal disorders		Screening for <i>Clostridium difficile</i> if diarrhoea, ancillary drugs if needed
	Cytopenia	Baseline and monthly complete blood count	

Table 13: Most important side effects of second-line drugs for MDR/RR-TB treatment and their management

DRUG	ADVERSE REACTIONS	MONITORING	MANAGEMENT
	Hepatotoxicity	Baseline and monthly liver enzymes	- Liver set < 3x ULN and absence of jaundice: continue medication, check for other causes & continue monitoring - Liver set > 5x ULN or > 3x ULN and symptoms: stop hepatotoxic drugs (non-hepatotoxic drugs only to be continued if at least 3 remaining drugs); rechallenge one by one once liver set is maximum < 2x ULN with close monitoring (at least twice weekly)
	Pruritus, rash, anaphylaxis		Ancillary medication if needed, topical treatment. Stop medication if severe reaction.
Bedaquiline			
	QTc-prolongation	ECG (baseline, weekly during the first month, then monthly)	Check for other QTc-prolonging drugs, check with cardiologist if QTc > 500ms
	Electrolyte imbalance	Baseline & monthly electrolytes (K ⁺ , Ca ²⁺ , Na ⁺ , Mg ²⁺ , HCO ₃ ⁻)	Electrolyte supplementation if needed
	Hepatotoxicity	Baseline and monthly liver enzymes	***
BPAL(M)-regimen (supplementary, individual drugs also discussed separate)			
	Pancreatitis	Baseline and monthly lipase & amylase	
	Lactic acidosis	Baseline and monthly HCO ₃	
	Renal toxicity	Baseline and monthly kidney function	
Clofazimine			
	Discolouration of skin and body fluids, ichthyosis, photo-sensibility	Avoid sun exposure, recommend use of sunscreen	
	Gastro-intestinal disorders		Ancillary medication if needed
	QTc-prolongation	ECG (baseline, weekly during the first month, then monthly)	Check for other QTc-prolonging drugs, check with cardiologist if QTc > 500ms Stop in the occurrence of intractable adverse events.
Cycloserine			
	Neuropsychiatric disturbances: Personality changes, psychosis, suicidal tendency, convulsions, vertigo, headache	Dose ramping at initiation Clinical and psychological evaluation at every visit	Stop in the occurrence of intractable adverse events
	Peripheral neuropathy	Clinical monitoring on peripheral neuropathy at each visit; pyridoxine 50 mg daily in primary prevention	Increase pyridoxine dose to 100 mg daily, encourage physical activity. Pharmacological treatment**
	Hepatotoxicity	Baseline and monthly liver enzymes	***
	Cutaneous hypersensitivity		Stop in the occurrence of intractable adverse events

Table 13: Most important side effects of second-line drugs for MDR/RR-TB treatment and their management

DRUG	ADVERSE REACTIONS	MONITORING	MANAGEMENT
Delamanid			
	QTc-prolongation	ECG (baseline, weekly during the first month, then monthly)	Check for other QTc-prolonging drugs, check with cardiologist if QTc > 500ms
	Gastro-intestinal disorders		Ancillary medication if needed
	Insomnia, vertigo		
Ethambutol			
	Optic neuritis	Baseline & monthly monitoring: testing visual acuity and colour discrimination	Referral to ophthalmologist if abnormal screening
Fluoroquinolone			
	Gastro-intestinal disorders		Ancillary medications if needed, no anti-acids within 2 hours of treatment
	Headache, dizziness		
	Transient mood changes		
	Mild QTc-prolongation	ECG (baseline, weekly during the first month, then monthly)	Check for other QTc-prolonging drugs, check with cardiologist if QTc > 500ms
	Tenosynovitis (including reports of Achilles tendinopathy and rupture)		
	Peripheral neuropathy	Clinical monitoring on peripheral neuropathy at each visit	Start pyridoxine 100mg daily, encourage physical activity. Pharmacological treatment**
	Aortic aneurysm and dissection		
	Hepatotoxicity*	Baseline and monthly liver enzymes	***
	Photo-toxicity	Avoid sun exposure, recommend use of sunscreen	
	Peripheral neuropathy	Clinical monitoring on peripheral neuropathy at each visit; pyridoxine 50 mg daily in primary prevention	Increase pyridoxine dose to 100 mg daily; encourage physical activity. Pharmacological treatment**
Linezolid			
	Cytopenia	a complete blood count baseline, every 1-2 weeks during first 6-8 weeks; afterwards monthly.	
	Peripheral neuropathy	Clinical monitoring on peripheral neuropathy at each visit	Reduce dose to 300 mg daily Encourage physical activity. Pharmacological treatment**
	Optic neuritis	Baseline & monthly monitoring: testing visual acuity and colour discrimination	Referral to ophthalmologist if abnormal screening
	Serotonergic syndrome		stop linezolid and adapt ancillary drugs before rechallenging
Meropenem			
	Cytopenia	Baseline and monthly complete blood count	
	Pruritus, anaphylaxis		Antihistaminic Anaphylaxis: stop treatment & referral to allergy specialist

Table 13: Most important side effects of second-line drugs for MDR/RR-TB treatment and their management

DRUG	ADVERSE REACTIONS	MONITORING	MANAGEMENT
	Diarrhoea		Screening for Clostridium difficile, ancillary drugs if needed
	Hepatotoxicity	Baseline and monthly liver enzymes	***
	Convulsions, delirium		
PAS			
	Gastro-intestinal disorders	Progressive increase of the dose	Split dose from qd to bid
	Hepatotoxicity	Baseline and monthly liver enzymes	***
	Cutaneous hypersensitivity		Stop in the occurrence of intractable adverse events
	Hypothyroidism	Baseline & 3-monthly TSH	Substitute with levothyroxine
	Cytopenia	Baseline and monthly complete blood count	
	Electrolyte imbalance	Baseline & monthly electrolytes (K ⁺ , Ca ²⁺ , Na ⁺ , Mg ²⁺ , HCO ₃ ⁻)	Electrolyte supplementation if needed
Pretomanid			
	Hepatotoxicity	Baseline and monthly liver enzymes	***
	Mild QTc-prolongation	ECG (baseline, weekly during the first month, then monthly)	Check for other QTc-prolonging drugs, check with cardiologist if QTc > 500ms
Prothionamide/Ethionamide			
	Gastro-intestinal disorders	Progressive increase of the dose	Split dose from qd to bid
	Hyper-salivation, metallic taste		
	Hepatotoxicity	Baseline and monthly liver enzymes	***
	Cutaneous hypersensitivity		Stop in the occurrence of intractable adverse events
	Hypothyroidism, gynecomastia.	Baseline & 3-monthly TSH	Substitute with levothyroxine
	Neuropsychiatric disturbances	Clinical and psychological evaluation at every visit	
	Peripheral neuropathy	Clinical monitoring on peripheral neuropathy at each visit; pyridoxine 50 mg daily in primary prevention	Increase pyridoxine dose to 100 mg daily Encourage physical activity. Pharmacological treatment**
Pyrazinamide			
	Hepatotoxicity	Baseline and monthly liver enzymes	***
	Hyperuricaemia	No standardised monitoring	Treat if symptomatic

* Moxifloxacin is potentially more hepatotoxic than Levofloxacin

** Pharmacological treatment of peripheral neuropathy caused by TB-medication: Gabapentin 300 mg (increase to 900 mg tid over 3 first days; titrated up to 1800 mg tid if needed (attention for AE especially if pre-existing renal insufficiency; If no effect or intolerance to Gabapentin then option to use Pregabalin: starting dose 50-75 mg bid, escalated to 150-300 mg bid. Low dose TCA (amitriptyline 25 mg qd at night) if no contraindication, to increase up to 150 mg qd (amitriptyline contraindicated with LZD for risk of serotonin syndrome), Carbamazepine 100-400 mg bid may also be an option (check for haematologic and liver toxicity).

*** 1/ Liver set < 3x ULN and absence of jaundice: continue medication, check for other causes & continue monitoring
2/ Liver set > 5x ULN or > 3x ULN and symptoms: stop hepatotoxic drugs (non-hepatotoxic drugs only to be continued if at least 3 remaining drugs); rechallenge one by one once liver set is maximum < 2x ULN with close monitoring (at least twice weekly)

6.9. Specific populations

6.9.1. Children (78, 79, 80)

In children there is few scientific evidence regarding management of MDR/RR-TB. Recommendations mainly rely on clinical experience and/or are extrapolated from adult data. As in non-resistant TB, it is of utmost importance to initiate appropriate treatment as early as possible to ensure good outcomes. In that context a swift referral to a paediatric TB-specialist is warranted.

Treatment will be based on the drug susceptibility test results, either from the adult index patient or from the microbiological data obtained from the child, since microbiological confirmation is achieved in fewer than 50 % of cases.

One should suspect drug resistance if a child worsens under standard regimen and/or if an adult source case had a bad treatment outcome (death, relapse or treatment failure).

The main principles are:

- Confirm MDR/RR-TB in the child, if possible
- Use the adult index case DST if no isolate from child is available
- Aim at the optimal dosage of every drug, eventually using therapeutic drug monitoring.
- International guidelines recommend now an all-oral regimen. Therefore, the use of second-line injectables will be limited to exclusive cases under the supervision of an experienced physician.
- Standardised short all oral regimens with weight-based dosing are the first choice if feasible.
 - As mentioned previously the BEAT-TB regimen containing bedaquiline, delamanid, linezolid, levofloxacin and clofazimine can be used in children of all ages. Same is true for following endTB-regimens: BDQ-LZD-Mfx-PZA or BDQ-LZD-Lfx-CFZ-PZA. Priority is given to the BEAT-TB regimen, as the shortest regimen is preferred in children.
 - The BPaL(M)-regimen is only recommended from the age of 14 years.
 - The longer 9-month all-oral regimens containing 7 different drugs 6BDQ-9Lfx(Mfx)-4Eto-4Hh-9E-9CFZ-9Z or 6BDQ-9Lfx(Mfx)-2LZD-4Hh-9E-9CFZ-9Z are good alternatives if none of the above-mentioned regimens are suitable.
- In very selected cases these standardised regimen are not feasible. In that case an individualised, tailored approach is indicated. This tailored regimen should respect following rules:
 - Initial regimen should include 4 to 5 drugs
 - Regimen should prioritise the WHO Group A and B drugs, as well as delamanid.
 - Bedaquiline and delamanid are approved in children of all ages.
- In case of CNS-TB, selection of drugs will be based on their ability to pass the blood-brain barrier.

- The duration of treatment depends on the site and severity of disease. Severe disease in children is defined as bilateral disease, cavitory disease, or extra-pulmonary disease other than cervical or intrathoracic lymphadenopathy without compression (82).
 - non-severe disease: 6 to 9 months
 - severe disease: 9 to 12 months, depending on the clinical progress
 - CNS-TB or osteo-articular TB: at least 12 months.

6.9.2. PLHIV, HCV, HBV

Specific aspects for PLHIV were discussed in the chapter on susceptible TB. These are no extra recommendations applicable to the MDR/RR forms of TB.

Treatment for hepatitis C should not be delayed but is preferably co-administrated with the anti-tuberculous drugs (82).

6.9.3. Pregnancy and breastfeeding

Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. These drugs are less frequently used in recent years with the arrival of newer drugs and drug regimens.

Knowledge about the safety of bedaquiline and delamanid in pregnancy and breastfeeding women is still sparse. In the BEAT-TB trial, these drugs (along with linezolid, levofloxacin and clofazimine) were used in pregnant/breastfeeding women, hence this is, up till now, the only treatment regimen in which bedaquiline and delamanid can be included. Data are lacking in regard of the BPAL(M) regimen, still contraindicated in pregnant or breastfeeding women.

The TB treatment outcomes, as well as the pregnancy outcome, and the postpartum surveillance for congenital anomalies should be documented to feed future recommendations for MDR/RR-TB treatment during pregnancy.

MANAGEMENT MDR/RR-TB:

Key points

1. Resistance to TB drugs arises from both intrinsic mechanisms, like bacterial membrane permeability and mutations, and extrinsic factors, including improper drug prescription, non-adherence, and drug interactions. Key risk factors include incomplete previous treatments, HIV infection, high bacterial load, and demographic factors such as age and socioeconomic status.
2. Early and rapid drug susceptibility testing (DST) is crucial for appropriate treatment. Recommended techniques include PCR and specific resistance tests for fluoroquinolone and other drugs.
3. Treatment Regimens (after agreement from the MDR-TB Expert Group)
 - Short regimens: for most cases of MDR/RR- and pre-XDR TB, all-oral six-month regimens using drugs like bedaquiline, pretomanid, linezolid and/or moxifloxacin or called BPaL(M) are effective. Other all-oral nine-months regimens containing bedaquiline can be an alternative if BPaL(M) is contraindicated.
 - Individualised longer regimens: typically for 18–20 months, used for complex cases where the shorter regimens are contraindicated
4. Routine follow-up involves clinical evaluation, laboratory monitoring, ECG for QT-prolonging drugs, and adverse event detection. Psychological support is advised due to treatment duration and potential side effects.
5. For children, PLHIV, pregnant or breastfeeding women, specific guidelines apply, such as using weight-based dosing for children and avoiding certain drugs in pregnancy.

7. Treatment of mono- and polyresistant TB

Resistance can be found to all first-line drugs, and the treatment regimen will need to be adapted according to the resistance profile based on DST results. In Belgium mono-resistance is present in 7,1 % of the TB cases with a majority of mono-resistance to isoniazid (6). Mono- and polyresistance other than RR and MDR will be discussed in this chapter.

7.1. Definitions

- Mono-resistance: resistance to one of the first-line TB drugs. In case of isoniazid mono-resistance, the international terminology is Hr-TB.
- Polyresistance: resistance to more than one of the first-line drugs, except for the combination of isoniazid and rifampicin which is defined as MDR-TB.

7.2. Medical management

Non-MDR/RR resistant TB usually does not entail complex management. It is of utmost importance though to have full DST results available, before adjusting the regimen. In case of any doubt, do not hesitate to contact the MDR-TB expert group of BELTA-TBnet (see practical aspects in the final chapter of this recommendation consensus).

7.2.1. Mono-resistance

- In case of mono-resistance to **ethambutol**, this drug can be skipped from the regimen. In the intensive phase, HRZ is continued and switched to continuation phase with HR as in fully susceptible TB. Be aware that detection of (presumed) ethambutol mono-resistance may be explained by NTM-coinfection, so it is worthwhile to perform testing for NTM in case ethambutol mono-resistance is detected. The treatment schedule is expressed as follows 2HRZ/4HR.
- Mono-resistance to **pyrazinamide** was already shortly discussed in the chapter on diagnosis of resistance. Susceptibility testing for PZA is not always performed either. It is important to realise that the result of the in vitro test does not always correlate with the in vivo efficacy of the antibiotic (cases of false resistance). An exception is *M. bovis*, which is naturally resistant to PZA. The following strategy is recommended:

- If a strain is PZA-susceptible: PZA should be used.
- If baseline DST shows isolated PZA-resistance, we then recommend excluding presence of *M. bovis* strain and/or perform alternative (e.g. genotypic) testing for PZA-resistance. Awaiting these results, treatment with PZA should be continued. In case of a true PZA-resistant or an *M. bovis* strain, treatment should be modified accordingly. The standard regimen recommended in that case is 9HR(E) (83).
- Mono-resistance to **isoniazid** is the most common form of mono-resistant TB. This resistance pattern is more common in patients with a prior history of TB treatment.

Since 2018, international recommendations have proposed a regimen composed of rifampicin, ethambutol, pyrazinamide and the addition of a second-generation fluoroquinolone (levofloxacin or moxifloxacin), replacing INH, for a total duration of 6 months after exclusion of FQ resistance via molecular DST. In patients with lower disease burden and/or increased risk of pyrazinamide toxicity, pyrazinamide can be stopped after 2 months (84, 85). Regarding the choice of fluoroquinolone, we suggest prioritising the use of levofloxacin due to the drug-drug interactions between rifampicin and moxifloxacin. Dosage is levofloxacin 750-1000 mg (10-15 mg/kg) qd or moxifloxacin 400 mg qd. The treatment schedule is expressed as follows 6FqREZ.

Since INH is not included in most rapid molecular DST tests, resistance results are often available one or more months after initiating the classical 4-drug regimen HRZE. It is recommended to test fluoroquinolone, through genotypic DST to have rapid confirmation (e.g. by using GeneXpert MTB/XDR that gives information, among others, on fluoroquinolone) of FQ susceptibility, before including a FQ in the treatment regimen. If genotypic DST shows no FQ-resistance, the second-generation FQ can be started. Phenotypic DST should be checked (results will come with delay) in order not to miss false negative resistance testing with the genotypic DST.

It is of course of utmost importance to exclude rifampicin resistance when isoniazid resistance is detected, but with the DST methods used in Belgium this information is standardly available in all cases. If Hr is detected late in the treatment course, repeat genotypic DST should be performed for all used drugs.

The 6-month duration starts counting as from the date fluoroquinolone is initiated in order to complete a 6-month course of a fluoroquinolone-containing regimen. In some cases, a total treatment duration of 6 months might be enough, especially in case of low disease burden or adverse events.

In case of associated fluoroquinolone-resistance, FQ-intolerance or contraindication for FQ (risk for prolonged QT-interval, pregnancy or breast-feeding even though neither are absolute contraindication), a 3-drug regimen of rifampicin, ethambutol and pyrazinamide is recommended for a total duration of 6 to 9 months (6-9RZE). Pyrazinamide must be prescribed the whole treatment duration as shorter use of pyrazinamide is associated with worse treatment outcome. In cases with more extensive disease treatment, extension to 9 months is associated with a better outcome and should be considered, especially if the treatment is well tolerated.

In children, scientific data is scarce, but the same treatment regimens are recommended as for adults.

7.2.2. Polyresistance (86)

- Patients with TB resistant to isoniazid and ethambutol should be treated with rifampicin, pyrazinamide, and a fluoroquinolone (levofloxacin or moxifloxacin, with preference for levofloxacin) for six to nine months (6-9FqRZ).
- Patients with TB resistant to isoniazid and pyrazinamide should be treated with rifampicin, ethambutol, and a fluoroquinolone (levofloxacin or moxifloxacin, with preference for levofloxacin) for 9 to 12 months (9-12FqRE).
- Patients with TB resistant to isoniazid, ethambutol and pyrazinamide should be treated with rifampicin, fluoroquinolone (levofloxacin or moxifloxacin, with preference for levofloxacin) and one or two additional oral agents to which the isolate is susceptible for a total duration of 9 to 12 months. Possible additional oral agents include ethionamide, linezolid or clofazimine. To optimise follow-up and management of these second-line drugs, referral to a specialist in TB-treatment is highly recommended.

Use of fluoroquinolone is the common denominator in this setting. Susceptibility testing for fluoroquinolone prior to using it is of utmost importance in all polyresistant strains.

For all polyresistant TB, treatment duration can be individualised to the rapidity of culture conversion. Consider giving a longer duration to patients with extensive disease, especially if treatment is well tolerated.

TREATMENT OF MONO- AND POLY RESISTANT TB:

Key points

1. Mono-resistance: resistance to a single first-line drug.
 - Isoniazid resistance (Hr-TB):
 - add a second-generation fluoroquinolone (preferably levofloxacin) to a regimen of rifampicin, ethambutol and pyrazinamide for 6 months after FQ-susceptibility has been confirmed by genotypic DST.
 - in cases of fluoroquinolone intolerance/contraindication/resistance, use a regimen of rifampicin, ethambutol and pyrazinamide for 6 months, potentially extended to 9 months.
 - Ethambutol resistance: omit ethambutol; continue HRZ regimen (isoniazid, rifampicin and pyrazinamide), then switch to HR for the continuation phase.
 - Pyrazinamide resistance:
 - Be aware of false resistance results: confirm with additional testing and perform strain identification to distinguish *MTBc* from *M. bovis*.
 - If confirmed, use a 9-month regimen of HR(E) (isoniazid, rifampicin, with/without ethambutol).
2. Polyresistance: resistance to multiple first-line drugs, other than the combination of isoniazid and rifampicin (which defines MDR-TB).
 - Isoniazid + ethambutol resistance: treat with rifampicin, pyrazinamide and a fluoroquinolone for 6–9 months.
 - Isoniazid + pyrazinamide resistance: treat with rifampicin, ethambutol and a fluoroquinolone for 9–12 months.
 - Isoniazid + ethambutol + pyrazinamide resistance: use rifampicin, a fluoroquinolone plus one or two additional effective oral agents for 9–12 months. Specialist referral is recommended for complex cases involving second-line drugs.
3. It is recommended to ask for advice to the national MDR-TB Expert Group (or at least one of its members) prior to any treatment modification.
4. Fluoroquinolones are commonly used in treating mono- and polyresistant strains; susceptibility testing is crucial.
5. Treatment duration should be tailored based on the extension and site of the disease and the rapidity of culture conversion.
6. Children: follow the same guidelines as adults despite limited scientific data.

8. Practical aspects

8.1. Reimbursement of drugs

First-line TB-drugs (except for rifampicin) are considered as Category A drugs. They are nearly entirely reimbursed by the national social security for patients with health insurance².

Rifampicin, as category B drug, needs the authorization from a medical officer of the patient's health insurance fund to be reimbursed. This request must be sent once the diagnosis is made and the quickest way to obtain authorization is to submit the request online via CIVARS (NL/FR).

Table 14: First-line drugs for treatment of drug-susceptible TB and reimbursement

Drug	Brand name	Preparation	Activity	INAMI/RIZIV Reimbursement
Isoniazid (INH)	Nicotibine®	30 Tablets of 300 mg	Bactericidal	100 % (Category A)
Rifampicin (RMP)	Rifadine®	100 Capsules of 150 mg 50 Capsules of 300 mg	Bactericidal and sterilizing	100 % (Category B)
Pyrazinamide (PZA)	Tebrazid ®	100 Tablets of 500 mg	Sterilizing	100 % (Category A)
Ethambutol (EMB)	Myambutol ®	100 Tablets of 400 mg	Bacteriostatic	100 % (Category A)

For patients without health insurance the intervention of BELTA-TBnet might be requested. More practical advice can be found on <https://www.belta.be/>.

Some additional drugs (e.g. pyridoxine) or drugs used in the management of side effects are not (fully) reimbursed by the social security. For these drugs, financial support can be provided by the BELTA-TBnet initiative.

Most second-line drugs are not reimbursed by the national social security system (e.g. bedaquiline) and some even must be imported from abroad (e.g. clofazimine, pretomanid, delamanid). Financial support for these drugs can be obtained through BELTA-TBnet. Approval of use of these drugs will be subject to revision of the (anonymised) patient file by the national MDR-TB Expert Group. To do so, you need to submit the BELTA-TBnet MDR registration form ([Annex 1](#)) and the BELTA-TBnet MDR expert advice form ([Annex 2](#)) at info@belta.be.

² Since January 2026, however, 2 € (1 € for patients with the BIM status) per box must be paid by the patients, whatever the reimbursement category is.

For all patients eligible to BELTA-TBnet, the patient needs to be registered online in <https://belta.be/> through the link formulaires/formulieren.

8.2. Optimisation of follow-up

Contact the local FARES or Respiratoire Gezondheid (VRGT) office for management of patients at risk of poor adherence via:

- FARES: <https://www.fares.be/contactCPT>
- Respiratoire Gezondheid (VRGT): [Centra in je buurt](#)³

Complex cases should be referred to a specialist with experience in management of TB. For advice regarding referral, one can contact the medical directors of both FARES and/or Respiratoire Gezondheid (VRGT).

In MDR/RR cases a treatment plan (**Annex 3**) is recommended to be used as a practical instrument throughout, as this might also facilitate communication between different caregivers and strengthen the subject's involvement.

8.3. High level long stay isolation ward

Since September 2019, Belgium has a specialised ward for TB patients who need a prolonged hospitalisation. This unit (Derscheid Unit) is localised on the hospital site of UMC St. Pieter/CHU St. Pierre in the heart of Brussels. For referral of a patient, one can reach out to the team by sending a request form (**Annexes 4** - [\[NL\]](#) / [\[FR\]](#)) to admissions808@stpierre-bru.be.

It is important to note that prior to admission, social coverage needs to be confirmed by the referring hospital.

8.4. IV-access management

For certain conditions, intravenous drugs may be administered over several months as a second-line treatment. Use of portal catheter, PICC-line or other vascular access device is recommended.

³ <https://www.respiratoiregezondheid.be/crgs>

8.5. TB-notification

8.5.1. Who should notify?

The laboratory where the diagnosis of TB is made.

The treating physician, especially when a diagnosis of TB disease is made without bacteriological confirmation (for instance where diagnosis is based on histopathological grounds) in order to have no one TB-case missed.

8.5.2. Procedure of notification?

In case of positive microbiological results, notification will be done by the laboratory. The treating physician must also report the case. In case treatment is initiated without microbiological confirmation of TB, based on clinical suspicion, this should also be done.

The procedure is different depending on the region:

> [In Flanders](#)⁴

In electronical medical file (EMD), by using the e-form 'Aangifte meldingsplichtige infectieziekte aan het Departement Zorg'

Through e-Healthbox (UMM). You can find Departement Zorg as 'Departement zorg - Team Infectieziekten' (1990001916) in the category 'Speciale door het eHealth-platform erkende entiteit'

Via an encrypted [email](#) by using [this document](#).

By phone: each province has its own telephone number which can be found through this link.

> [In Wallonia](#)⁵

through the AViQ notification platform [Trace in Wall](#)⁶

by phone: 071/33.77.77

by encrypted [email](#)

by contacting FARES.

⁴ <https://www.departementzorg.be/nl/een-meldingsplichtige-infectieziekte-aangeven>

⁵ <https://www.aviq.be/fr/prevention-maladies/maladies-infectieuses/declaration-obligatoire>

⁶ https://ga.aviq.be/Home/Index?ReturnUrl=TraceInWal %2525_ %2525 %25252F

> [In Brussels \[FR\]](#)⁷ / [\[NL\]](#)⁸

From the electronical medical file, by using an eForm: 'Déclaration des maladies infectieuses à Vivalis (GGC)' or 'Aangifte meldingsplichtige infectieziekte aan Vivalis (GGC)'

As an alternative you can send this form [\[FR\]](#) / [\[NL\]](#):

- Either via e-Healthbox (UMM), you can find Vivalis (1990007260) in the category 'Speciale door het eHealth-platform erkende entiteit' or 'Entité spéciale reconnue par la plateforme eHealth'
- Either by encrypted email notif-hyg@vivalis.brussels

By contacting Respiratoire Gezondheid (VRGT) and/or FARES.

8.6. Therapeutic Drug monitoring

In Belgium this can be performed in the LHUB-ULB lab. Clinical biology pharmacist David Fage is the contact person in this lab. There is a delay of 2 weeks to obtain the results. Tests can be requested by using a specific form ([Annex 5](#)).

8.7. MDR Expert advice

Templates to be used can be found in annexes 1 and 2 to be sent to info@belta.be.

7 <https://www.vivalis.brussels/fr/prevenir-et-agir/surveillance-sanitaire/maladies-a-declaration-obligatoire-en-region-bruxelloise>

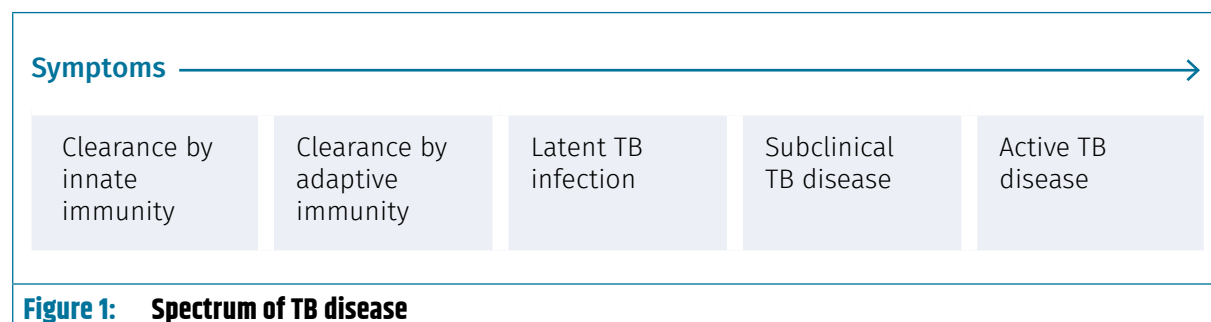
8 <https://www.vivalis.brussels/nl/preventie/gezondheidstoezicht/meldingsplicht-voor-infectieziekten-in-het-brussels-gewest>

Addendum: Pathophysiology of TB

1. Natural history

TB is commonly considered as a pulmonary disease. It is thought that infection with droplets containing *Mycobacterium TB* leads to primary disease in 5-10 % of infected cases while the rest of them will develop TB infection defined as presence of immunoreactivity to TB antigens in absence of symptoms or radiologic signs of TB. Reactivation is thought to occur in 5-10 % of the patients with TB infection, mainly in the first two years after the infection.

The former binary definition of latent versus active TB classified a person either as having latent or active TB, with no possible distinction whether a person has cleared the infection or remains with viable mycobacteria in the body that cause no symptoms (= latent) or active TB. It has been proposed that TB is better described as a spectrum of disease, going from elimination of the infection mediated by innate and adaptive immune response to infection controlled with some viable non-replicating bacteria to controlled bacterial replication with subclinical symptoms to frank clinical disease.⁹



The concept of TB as a pulmonary disease has also been challenged. It has been proposed that TB may be viewed as a lymphatic disease with a pulmonary portal.¹⁰ According to this theory, *MTBc* passes asymptotically through the lungs while establishing infection in the lymphatic system. This may explain why primary infection and reactivation often occur at distinct anatomical sites (Gohn lesion during the primary infection, while reactivation usually occurs at the lungs apex).

9 Barry CE 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, Schnappinger D, Wilkinson RJ, Young D. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol*. 2009 Dec;7(12):845-55. doi: 10.1038/nrmicro2236. Epub 2009 Oct 26. PMID: 19855401; PMCID: PMC4144869.

10 Behr MA, Waters WR. Is tuberculosis a lymphatic disease with a pulmonary portal? *Lancet Infect Dis*. 2014 Mar;14(3):250-5. doi: 10.1016/S1473-3099(13)70253-6. Epub 2013 Nov 22. PMID: 24268591.

2. Human immunologic response to MTBc infection

INNATE IMMUNOLOGIC RESPONSE TO MTBC INFECTION ¹¹

After inhalation, *MTBc* must overpass the airways. The airway ciliated epithelial cells recognize the pathogen modifying the surface airway liquid properties and impeding the passage.

Alveolar macrophages

Once in alveolar space, *MTBc* is phagocytised by alveolar macrophages. Their role is ambivalent: if AM engulf the bacteria into phagosomes and, if appropriately activated, can destroy them providing an effective immune defence; otherwise, they become a niche for the pathogen, allowing *MTBc* to replicate and persist in a latent phase.¹² Successful elimination of *MTBc* occurs through phagosome maturation, lysosome fusion, or autophagy, aided by vitamin D, IFN- γ , and IL-12. However, *MTBc* has evolved numerous mechanisms to survive inside macrophages. For example, the secreted virulence factor ESAT-6 disrupts phagosome maturation, blocking the phagolysosomal fusion that would normally acidify and digest the bacteria. Reactive oxygen species help to kill the pathogen, but *MTBc* resists with mycolic acids and enzymes. A battle for metals like zinc, copper, iron, and manganese also occurs within the phagosome, critical to controlling the infection. The human host can overcome the infection only in its early stages without medication.

Natural killer cells

NK cells exert direct cytotoxicity (destroying *MTBc*-infected cells before the bacteria can spread) and immunomodulatory functions. NK cells secrete IFN- γ and IL-22, among other cytokines. IFN- γ from NK cells increases macrophage activation, and IL-22 has been shown to inhibit intracellular *MTBc* growth by promoting phagolysosomal fusion in infected macrophages. NK cells also interact with dendritic cells and influence T-cell responses, essentially “priming” the adaptive immune system. Through these actions, NK cells help curb early infection, although *MTBc* can evade NK recognition to some degree.

Neutrophils

This type of immunologic cell is mainly an effector. The contact with some *MTBc* proteins provokes intracellular calcium flood, necrosis, and exteriorisation of neutrophil extracellular traps, which are potent anti-microbic agents. Moreover, during a respiratory burst, neutrophils release enzymes (e.g. elastase and myeloperoxidase) capable to damage both *MTBc* and lung tissues.

Dendritic cells

These cells are part of the bridge between innate and adaptive immunity. DC efficiently present the antigen, co-stimulate, and produce cytokines organising a specific immune response against *MTBc*.

ADAPTIVE IMMUNOLOGIC RESPONSE TO MTBC INFECTION

The trained immune response starts with T-lymphocyte priming by antigen-presenting cells in the lymph nodes. A delay in this process increases host susceptibility.¹³ *MTBc* disrupts CD40 binding, hindering T-lymphocyte interaction with dendritic cells. CD4⁺ T-helper 1 cells are key in controlling *MTBc* growth, but by the time they are activated, eradicating the infection without

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medication is impossible. A delayed hypersensitivity response (TST) occurs 3 to 8 weeks after infection if the immune response is triggered.

T-lymphocytes CD4+

Through the IL-12 pathway, DCs activate antigen-specific lymphocytes CD4+ T helper 1, which migrate from the lymph nodes to the lung. The main role of this specific lymphocyte is the production of INF- γ . This cytokine has limited direct antimicrobial activity, but it improves phagosome maturation and enhances the cytotoxic activity of CD8+ T-lymphocytes (Figure 2). Patients affected by active lung TB produce lower levels of INF- γ , which are partially restored after treatment initiation.¹⁴

T-lymphocytes CD8+

This lymphocyte line has an effector action. The contact with an *MTBc* infected cell mediates its destruction via apoptosis. Furthermore, CD8+ T-lymphocytes can also present *MTBc* antigen through class 1 major histocompatibility complex and produce cytokines such as TNF- α , IL-2, and IFN- γ . Finally, the same lymphocyte can manufacture IL-10 and TGF- β , which limit immune response.

THE GRANULOMA FORMATION

After adaptive immunity is established, granulomas form as the host attempts to contain an uncontrollable infection. However, *MTBc* can persist in a latent state, with reactivation occurring in 10-20 % of cases due to factors like immunocompromised status, malnutrition, stress, or aging. Granuloma rupture may release *MTBc* into the airway, leading to infection. Initially, *MTBc* triggers an inflammatory response with M1 macrophages producing IL-6, IL-12, and TNF- α , which aids granuloma formation. *MTBc* then switches macrophages to an anti-inflammatory M2 phenotype through ESAT6, ensuring its survival. The granuloma's core contains bacteria, dying macrophages, and is surrounded by immune cells like macrophages (some of them become multinucleate giant cells also known as Langhans cells), T and B lymphocytes, and neutrophils.^{15,16}

3. Pathogenesis of drug-resistant TB

Resistance in *MTBc* is almost exclusively caused by mutations in the mycobacterial DNA leading to drug target alteration, over-expression of drug target, disruption of prodrug activation and the activation of efflux pumps.¹⁷

Drug resistance arises when the bacteria are subjected to incomplete drug pressure or after transmission of a drug-resistant strain. Incomplete drug pressure can be the consequence of poor compliance, weak treatment regimens, or altered bioavailability of the drug (malabsorption, drug-drug interactions).

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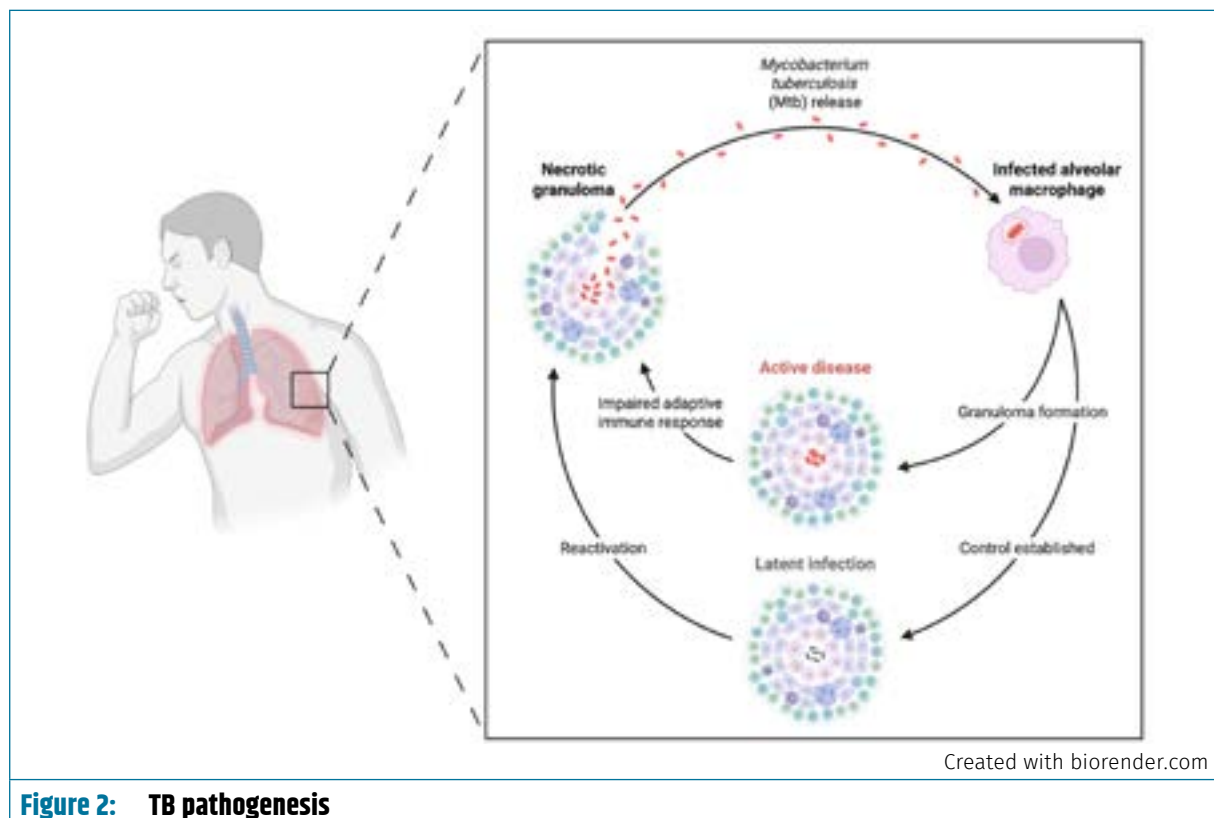


Figure 2: TB pathogenesis

PATHOPHYSIOLOGY:

Key points

1. TB is traditionally seen as a pulmonary disease, but new insights suggest it may also function as a lymphatic disease with a pulmonary portal.
2. TB infection begins when airborne *MTBc* reaches the lungs, causing active disease in 5-10 % of cases, with TB infection developing in others. TB infection can reactivate in certain patients, especially within two years of infection, leading to a spectrum of disease severity.
3. The immune response to TB involves both innate and adaptive immunity.
4. Granulomas form to contain TB, but if ruptured, they can release bacteria, leading to active disease. *MTBc* uses mechanisms like switching macrophages to anti-inflammatory types to survive within these structures.
5. Drug-resistant TB results from mutations in mycobacterial DNA, poor drug compliance, or inadequate treatment. This resistance can occur due to incomplete drug pressure or transmission of a resistant strain.

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Annexes

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Formulaire d'enregistrement MDR

À renvoyer à: BELTA-TBnet, Rue Haute, entrée 290,807a 1000 Bruxelles
Tel: 02-518 18 19 - E-mail: info@belta.be

Données personnelles du patient

Nom				Prénom			
Numéro d'identification national					Sexe	☐ Masculin ☐ Féminin	
Date de naissance				Pays de naissance			
Nationalité				Date d'arrivée en Belgique			
Pays d'origine de la famille					Dossier BELTA		
Adresse							
Groupe à risque (vous pouvez cocher plus d'une réponse)	☐ Prisonnier ☐ Demandeur d'asile ☐ Illégal ☐ Sans-abri ☐ Défavorisé ☐ Contact récent (<2 ans) avec un malade atteint de TB contagieuse ☐ Contact avec un patient MR connu ☐ Personne travaillant avec un groupe à risque ☐ Travailleur médico-social (y compris stagiaire et bénévole) ☐ Autre: ☐ Aucun ☐ Inconnu			Facteurs de risque (vous pouvez cocher plus d'une réponse)	☐ Alcoolisme chronique ☐ Malnutrition (>10% sous le poids idéal) ☐ Diabète ☐ Immunosuppression à la suite d'une maladie ou d'une prise de médicaments ☐ Insuffisance rénale ☐ Lésions fibrotiques à la radiographie du thorax ☐ Pneumoconiose (silicose, etc.) ☐ Carcinome de la tête ou du cou, leucémie, maladie de Hodgkin ☐ Toxicomane IV ☐ Fumeur ☐ Expatrié qui a séjourné/séjourne depuis longtemps dans une région endémique ☐ Autre: ☐ Aucun ☐ Inconnu		
	Résultat du test VIH	☐ Positif ☐ Négatif ☐ Inconnu					
Antécédents de TB		☐ Oui (voir ci-dessous. Vous pouvez indiquer plus d'un antécédent) ☐ Non ☐ Inconnu					
Année	Pays		Traitement (schéma, durée) et autres informations				

Informations concernant le diagnostic de l'épisode actuel de tuberculose

Date du diagnostic						
Type de TB	☐ Pulmonaire (P) ☐ Extrapulmonaire (EP) ☐ P & EP	Si EP ou P & EP: localisation EP (vous pouvez donner plus d'une réponse)				
Résultats bactériologiques	Examen microscopique direct	PCR		Culture	Genexpert	
Date prélèvement						
Type d'échantillon						
Résultat	☐ Positif ☐ Négatif ☐ Inconnu	☐ <i>M. tuberculosis</i> ☐ <i>M. tuberculosis</i> complex ☐ <i>M. bovis</i> ☐ <i>M. africanum</i> ☐ Négatif/Inconnu		☐ Pas encore disponible ☐ Positif ☐ Négatif ☐ Inconnu	☐ Négatif / Inconnu ☐ <i>M. tuberculosis</i> + / Absence résistance rifa ☐ <i>M. tuberculosis</i> + / Présence résistance rifa	
Résistance médicamenteuse	Antibiogramme phénotypique	Whole genome sequencing		Line Probe Assay MTBDRplus & MTBDRsl		
Date prélèvement						
Type d'échantillon						
Labo						
	S = sensible R = résistant 0 = inconnu	Cochez si présence mutation	Type de mutation		Cochez si présence mutation	Type de mutation
Rifampicine		☐		<i>rpoB</i>	☐	
Isoniazide		☐		<i>katG</i> <i>inhA</i>	☐ ☐	
Éthambutol		☐				
Pyrazinamide		☐				
Rifabutine		☐				
Ofloxacin		☐		<i>gyrA</i>	☐	
Moxifloxacin		☐		<i>gyrB</i>	☐	
Streptomycine		☐				
Kanamycine		☐		<i>rrs</i>	☐	
Amikacine		☐		<i>eis</i>	☐	
Capréomycine		☐				
E-/Prothionamide		☐				
Cyclosérine		☐				
PAS		☐				
Linézolid		☐				
Clofazimine		☐				
Bédaquiline		☐				
Délamanid		☐				
Si réalisation d'un examen anatomo-pathologique	Date	Type d'échantillon	Résultat			

[illegible]

Responsables du suivi du patient

Spécialiste assurant le suivi du patient à l'hôpital		
Nom	Hôpital (nom + commune + service où travaille le médecin)	
Éventuellement généraliste ou autre médecin assurant le suivi du patient en ambulatoire		
Nom	Adresse	Téléphone et adresse électronique
Unité veillant à l'observance du traitement		
Nom de l'unité	Nom du responsable	Téléphone et adresse électronique si unité différente de la VRGT ou du FARES

Détails concernant l'enregistrement dans BELTA-TBnet (A remplir uniquement si aucun formulaire d'enregistrement BELTA-TBnet n'a été rempli)

Date d'enregistrement dans BELTA-TBnet		
Motif de prise en charge par BELTA-TBnet		Catégorie de prise en charge
☐ Demandeur d'asile ☐ Illégal ☐ Couverture sociale non (encore) régularisée (donnez davantage d'informations ci-dessous) ☐ Patient multirésistant avec une mutuelle ☐ Touriste ☐ Etudiant étranger ☐ Patient non multirésistant avec une mutuelle et traité avec des médicaments de 2ème ligne (donnez davantage d'informations ci-dessous) ☐ Patient non multirésistant ayant une mutuelle et qui ne peut pas payer sa participation personnelle. Spécifiez: (vous pouvez cocher plus d'une réponse) ☐ pyridoxine ☐ médication pour effets secondaires ☐ préparation magistrale ☐ traitement préventif à la rifadine® ☐ ticket modérateur consultations et/ou examens		☐ Traitement antituberculeux ☐ Traitement préventif ☐ Diagnostic
☐ Autre:		
Informations complémentaires		

Complété par le

MDR Registratieformulier



Op te sturen aan: BELTA-TBnet, Hoogstraat 290,807a, 1000 Brussel
Tel: 02-518 18 19 - E-mail: info@belta.be

Patiëntengegevens

Naam			Voornaam		
Nationaal identificatienummer			Geslacht	☐ Man	☐ Vrouw
Geboortedatum			Geboorteland		
Nationaliteit			Datum aankomst België		
Land van oorsprong van de familie			Tel.		
Adres					
Risico-groep (u mag meer dan 1 groep aan-vinken)	☐ Gedetineerde ☐ Asielzoeker ☐ Illegaal ☐ Dakloos ☐ Kansarm ☐ Recent (<2 j) contact met besmettelijke TB patiënt ☐ Contact met gekende MDR patiënt ☐ Werkend met een risicogroep ☐ Gezondheidswerker (incl. stagiair en vrijwilliger) ☐ Andere: ☐ Geen ☐ Onbekend		Risico-factor (u mag meer dan 1 factor aan-vinken)	☐ Chronisch alcoholisme ☐ Ondervoeding (>10% onder ideaal lichaamsgewicht) ☐ Diabetes mellitus ☐ Immunosuppressie ten gevolge van ziekte of geneesmiddelen ☐ Nierinsufficiëntie ☐ Fibrotische lesies op RX thorax ☐ Pneumoconiose (silicose e.a.) ☐ Hoofd- of halscarcinoma, leukemie, Hodgkin lymfoma ☐ IV druggebruiker ☐ Roker ☐ Persoon uit niet-endemisch land die lang verbleef in endemisch gebied ☐ Andere: ☐ Geen ☐ Onbekend	
	HIV resultaat	☐ Positief ☐ Negatief ☐ Onbekend			
TB antecedenten	☐ Ja (zie hieronder. U kan meer dan 1 antecedent opgeven) ☐ Nee ☐ Onbekend				
Jaar	Land	Behandeling (schema, duur) en andere gegevens			

Gegevens betreffende de diagnose van de huidige TB episode

Datum van diagnose						
Type TB	☐ Pulmonaal (P) ☐ Extra-pulmonaal (EP) ☐ P & EP	Indien EP of P & EP: localisatie EP (u mag meer dan 1 localisatie opgeven)				
Bacteriologische resultaten	Rechtstreeks microscopisch onderzoek	PCR	Cultuur	Genexpert		
Datum staalafname						
Type staal						
Resultaat	☐ Positief ☐ Negatief ☐ Onbekend	☐ <i>M. tuberculosis</i> ☐ <i>M. tuberculosis</i> complex ☐ <i>M. bovis</i> ☐ <i>M. africanum</i> ☐ Negatief/Onbekend	☐ Nog niet beschikbaar ☐ Positief ☐ Negatief ☐ Onbekend	☐ Negatief/Onbekend ☐ <i>M. tuberculosis</i> + / Geen resistentie rifa ☐ <i>M. tuberculosis</i> + / resistentie rifa aanwezig		
Geneesmiddelen-resistentie	Fenotypisch antibiogram	Whole genome sequencing		Line Probe Assay MTBDRplus & MTBDRsl		
Datum staalafname						
Type staal						
Labo						
	S = gevoelig R = resistent O = onbekend	Vink aan indien mutatie	Type mutatie		Vink aan indien mutatie	Type mutatie
Rifampicine		☐		<i>rpoB</i>	☐	
Isoniazide		☐		<i>katG</i> <i>inhA</i>	☐ ☐	
Ethambutol		☐				
Pyrazinamide		☐				
Rifabutine		☐				
Ofloxacin		☐		<i>gyrA</i> <i>gyrB</i>	☐	
Moxifloxacin		☐			☐	
Streptomycine		☐				
Kanamycine		☐		<i>rrs</i> <i>eis</i>	☐	
Amikacin		☐			☐	
Capreomycine		☐				
E-/Prothionamide		☐				
Cycloserine		☐				
PAS		☐				
Linezolid		☐				
Clofazimine		☐				
Bedaquiline		☐				
Delamanid		☐				
Indien anatomopathologisch onderzoek plaatsvond	datum	specimen	resultaat			

BELTA-TBnet MDR registratieformulier

Opvolging van de patiënt

Arts verantwoordelijk voor de opvolging van de patiënt		
Naam arts	Ziekenhuis (naam + gemeente, + afdeling waar arts werkt)	
Unit die de behandelingsgetrouwheid van de patiënt opvolgt		
Naam unit	Naam verantwoordelijke	Telefoon en e-mail adres indien niet VRGT of FARES

Details BELTA-TBnet registratie (enkel in te vullen indien nog geen gewoon BELTA-TBnet registratieformulier werd ingevuld)

Datum start BELTA-TBnet			
Reden van ten laste neming door BELTA-TBnet (vink 1 reden aan)			Categorie van ten laste neming
☐ Asielzoeker ☐ Illegaal ☐ Sociale dekking (nog) niet geregulariseerd (geef bijkomende uitleg hieronder) ☐ MDR met mutualiteit ☐ Toerist ☐ Buitenlands student ☐ Niet-MDR met mutualiteit die behandeld wordt met tweedelijns-geneesmiddelen (geef bijkomende uitleg hieronder) ☐ Niet-MDR met mutualiteit die eigen aandeel niet kan betalen.			☐ TB behandeling ☐ Preventieve therapie ☐ Diagnose
➡ Specificeer: ➡ (u mag meer dan 1 aanvinken)			☐ pyridoxine ☐ medicatie nevenwerkingen ☐ magistrale bereiding ☐ preventie met rifadine ☐ remgeld raadplegingen en/of onderzoeken
✎ Andere:			
Bijkomende uitleg			

Ingevuld door op

STANDARD FORM MDR

Patient profile

Sex: Birth: Age: Nationality: Land of origin: Type TB: Name treating clinician:	
--	--

Clinical data

Tb-diagnose: previous history of TB: MDR-TB diagnose: HIV-status: At risk group: Start hospitalisation: End hospitalisation:	
--	--

Diagnostic data

Date of sample collection: Type of sample: <u>Result</u> Microscopic : MGIT-DST : Xpert MTB/Rif Xpert/MTB/XDR : WGS :	
---	--

Dr. HOSPITAL NAME

VRGT/FARES GP

FOLLOW UP		hospitalisations (add dates)	sputum conversion (add exact date)															
MICROBIOLOGY EVOLUTION	SPECIMEN	year																
	AURAMINE	jan	feb	mrt	apr	mei	jun	jul	aug	sep	okt	nov	dec	jan	feb	mrt	apr	mei
	CULTURE																	
	weight (kg)																	
HOSPITALISED																		

TREATMENT PLAN	treatment plan (add dose)	R resistant	I intermediate resi
----------------	--	----------------------------------	--

GENO R mutation		FENO R 1st 2nd	year																
			jan	feb	mrt	apr	mei	jun	jul	aug	sep	okt	nov	dec	jan	feb	mrt	apr	mei
H ^h	inhA																		
	katG																		
	mshA																		
	rpoB																		
R	rpoB																		
	rpoB																		
	gvrB																		
	gvrB																		
A	Bdg																		
	Lzd																		
	Cfz																		
	Trd																		
B	E																		
	embA																		
	Dlm																		
	pncA																		
C	lpm-Clm																		
	Mpm-Clv																		
	Am																		
	(S)																		
	eto																		
	inhA																		
	inhA																		
	Pas																		
	Pto																		
	Pas																		
	Pto																		
	Pto																		

PLANNED INVESTIGATIONS
..../...:
..../...:

RELATIVES
name + phone

STANDARD FORM MDR

Recommended treatment by MDR-TB Expert group

Consensus: Prescribed regimens: Start MDR-TB treatment : End MDR-TB treatment: Day of delay in start of MDRTB treatment:	
---	--

Serious Adverse event

--

Patients follow up

Compliance:  Clinical evolution: Radiological evolution: Bacteriological evolution: Treatment: Outcome:	
--	--

[illegible]

Unité 808

DEMANDE D'ADMISSION

RENSEIGNEMENTS ADMINISTRATIFS

Nom/Prénom :

Date de naissance:

Sexe : M – F

NISS :

Adresse :

Nationalité et langue :

Personne de contact (famille, proche) :

Etiquette

Situation :

O Séjour légal

O Séjour irrégulier

O Demandeur de protection internationale

O SDF

O Centre d'hébergement, Fedasil, maison d'accueil...

O Touriste :

O Ressortissant UE :

O Autre (mentionner) :

Assurabilité :

O Mutuelle + n° Fédération :

O Assurance privée

Références de l'assurance :

CT1/CT2

O Médiprima (**doit être en ordre avant l'admission**)

O Autre (mentionner) :

O CEAM, certificat

Si S2, autorisation + hôpital

Validité (12 mois) :

Si réquisitoire (**Le demande du réquisitoire doit avoir été introduite avant le transfert du patient**) :

O CPAS :

O Autre (mentionner) :

O FEDASIL :

O Prison :



Si CPAS/FEDASIL :

N° dossier CPAS/FEDASIL / n° SP :

Coordonnées de l'AS de référence :

Nom/Prénom :

N° de tél. :

Adresse e-mail :

Hôpital demandeur**Assistant.e social.e référent.e à contacter**

Nom/Prénom :

N° de tél. :

Adresse e-mail :

Médecin(s) et personnel soignant (dont FARES/VRGT) de référence à contacter

Nom/Prénom :

N° de tél. :

Adresse e-mail :

Nom/Prénom :

N° de tél. :

Adresse e-mail :

Annexes à joindre par le service social

- Copie des documents d'identité : Carte id. ; carte orange ; passeport ; cachet ; visa ; etc.
- Annexe 26
- Documents d'assurabilité (CEAM, ...)

Assistante sociale référente Département maladies infectieuses - U808 – CHU Saint-Pierre Bruxelles

LINTERMANS Alizé

Tél. 02/535.37.29

Mail : alize.lintermans@stpierre-bru.be



La demande d'admissions doit être adressée à l'adresse suivante : **admissions808@stpierre-bru.be**

INFORMATIONS MEDICALES

Historique de la tuberculose actuelle

- Date diagnostic :

- Localisation :

- Date début traitement :

- Examen direct expecto au moment de la demande de transfert ☐ positif ☐ négatif ☐ : inconnu

- *Motif du transfert à l'unité de long séjour*

Tuberculose multi-résistante

Contagiosité prolongée (> 3 semaines de traitement)

Prise en charge ambulatoire jugée impossible

Echec de prise en charge ambulatoire (mauvaise compliance, arrêt du suivi)

Patient sans-abri ne pouvant être logé en maison d'accueil

Patient sans-abri, en attente de logement en maison d'accueil

Critères cliniques d'admission

- Patient cliniquement stable

- Surveillance médicale continue non nécessaire

- Autonomie pour la mobilisation, l'alimentation et les soins d'hygiène

- Frottis de screening MRSA récents négatifs

- Frottis anal récent négatif pour bactéries multi-résistantes (VRE, BLSE +, CPE +)

Principaux antécédents médicaux

Assuétudes



Principaux antécédents psychiatriques pathologies psychiatriques actives

INFORMATIONS INFIRMIERES

HYGIÈNE

☐ Autonome ☐ Aide nécessaire

ALIMENTATION

☐ Satisfaisante, orale ☐ Artificielle : entérale ☐

DEGRE D'AUTONOMIE

☐ Se mobilise seul ☐ Alitement fréquent ☐ Artificielle : parentérale Avec aide ☐ Alitement continu

PEAU ET MUQUEUSES

Escarres OUI NON
Plaies OUI NON

RESPIRATION

Dyspnée : ☐ d'effort de repos
Encombrement Oxygène intermittent / continu Epanchement
pleural Trachéotomie placée le :

NEUROPSY

☐ Anxiété ☐ Dépression ☐ Démence

CATHÉTERS

Periphérique Central ☐ Pic line
Port-a-cath Sonde vésicale

VALIDATION PAR INFECTIOLOGUE RESPONSABLE

Oui : Dr

Non :

Signature du demandeur :



Unit 808

AANVRAAG VOOR OPNAME

ADMINISTRATIEVE INLICHTINGEN:

Naam/Voornaam:

Geboortedatum:

Geslacht: M - V

INSZ:

Adres:

Nationaliteit en taal:

Contactpersoon (familie, vriend):

Kleefzegel

Situatie:

☐ Wettelijk verblijf

☐ Illegaal verblijf

☐ Aanvrager internationale bescherming

☐ Dakloos

☐ Wooncentrum, Fedasil, opvangcentrum ...

☐ Toerist:

☐ EU-onderdaan:

☐ Andere (specificeer):

Verzekerbaarheid:

☐ Ziekenfonds + nummer:

CT1/CT2

☐ Mediprima (moet in orde zijn vóór de opname)

☐ Privéverzekering

Verzekeringsreferenties:

☐ Andere (specificeer):

☐ EZVK, certificaat ...

Geldigheid (12 maanden):

Indien s2, toestemming + ziekenhuis



Indien betalingsverbintenis (het verzoek voor de betalingsverbintenis moet zijn ingediend voordat de patiënt wordt overgeplaatst):

O OCMW:

O Andere (specificeer):

O FEDASIL:

O Gevangenis:

Indien OCMW/FEDASIL:

Dossiernr. OCMW/FEDASIL / nr. BS:

Contactgegevens van de referentie-MW:

Naam/Voornaam:

Telefoonnr.:

E-mailadres:

Aanvragend ziekenhuis

Referentie-maatschappelijk werker met wie contact moet worden opgenomen

Naam/Voornaam:

Telefoonnr.:

E-mailadres:

Referentiearts(en) en verplegend personeel (inclusief FARES/VRGT) met wie contact moet worden opgenomen

Naam/Voornaam:

Telefoonnr.:

E-mailadres:

Naam/Voornaam:

Telefoonnr.:

E-mailadres:

Bijlagen toe te voegen door de sociale dienst

- Kopie van identiteitsdocumenten: identiteitskaart; oranje kaart; paspoort; stempel; visum; enz.
- Bijlage 26
- Verzekeraarsdocumenten (EZVK, enz.)

Referentie-maatschappelijk werker Infectieziekten - U808 - UMC Sint-Pieter Brussel

Alizé LINTERMANS

Tel. 02/535.37.29

E-mail: alize.lintermans@stpierre-bru.be

De aanvraag voor opname moet naar het volgende adres worden gestuurd: **admissions808@stpierre-bru.be**



MEDISCHE INFORMATIE

Geschiedenis van de huidige

tuberculose

- Datum diagnose:

- Locatie:

- Begindatum behandeling:

- Sputumonderzoek op het moment van de
overplaatsingsaanvraag: onbekend

☐ positief ☐ negatief ☐

- Reden voor overplaatsing naar de eenheid voor langdurig verblijf

Multiresistente tuberculose

Langdurige besmettelijkheid (> 3 weken behandeling)

Ambulante zorg onmogelijk geacht

Ambulante zorg mislukt (slechte therapietrouw, stopzetten van de opvolging)

Dakloze patiënt kan niet in een opvangcentrum worden ondergebracht

Dakloze patiënt in afwachting van huisvesting in een opvangcentrum

Klinische criteria voor opname

- Patiënt klinisch stabiel

- Continu medisch toezicht niet nodig

- Kan zelfstandig bewegen, eten en zichzelf verzorgen

- Recente uitstrijkjes MRSA-screening negatief

- Recent anaal uitstrijkje negatief voor multiresistente bacteriën (VRE, BLSE +, CPE +)

Medische voorgeschiedenis

Gewoontes

Belangrijkste psychiatrische voorgeschiedenis Actieve psychiatrische pathologieën



VERPLEEGKUNDIGE INFORMATIE

HYGIËNE

☐ Zelfstandig ☐ Hulp nodig

VOEDING

☐ Bevredigend, oraal ☐ Kunstmatig: enteraal ☐

MATE VAN ZELFSTANDIGHEID

☐ Kan zonder hulp bewegen ☐ Regelmatige bedrust ☐ Kunstmatig: parenteraal
☐ Met hulp ☐ Continue bedrust

HUID EN SLIJMVLIEZEN

Doorligwonden JA NEE
Wonden JA NEE

ADEMHALING

Dyspneu: ☐ inspanning in rust
Pleurale Zuurstof intermitterend / continu Effusie geplaatst
obstructie Tracheotomie op:

NEUROPSYCHOLOGIE

☐ Angst ☐ Depressie ☐ Dementie

KATHETERS

Perifeer Centraal ☐ PICC-
Port-a-cath Sonde katheter blaas

VALIDATIE DOOR DE VERANTWOORDELIJKE INFECTIOLOOG

Ja Dr.

NEE:

Handtekening van de aanvrager:





TDM OF ANTITUBERCULOSIS DRUGS

MANDATORY
Request N°

FROM (Laboratory Information)

TO:

LHUB-ULB, Service de Chimie Médicale
Rue Haute 322
1000 Bruxelles
Belgique

MANDATORY

Patient information

Surname, first name:

Date of birth: JJ / MM / AAAA

Sexe: ☐ F ☐ M

Address:

MANDATORY

Request date: JJ / MM / AAAA

Stamp and signature of Doctor:

Main indications of TDM

- ☐ Gastro-intestinal abnormalities (*malabsorption, chronic diarrhea, gastric bypass, etc.*)
- ☐ Drug-drug interactions
- ☐ HIV +
- ☐ Diabetes
- ☐ Drugs-related toxicity
- ☐ Renal insufficiency
- ☐ Absence of culture conversion after 2 months of therapy
- ☐ Second-line drugs therapy
- ☐ Monitoring of high dosage isoniazid
- ☐ Monitoring post-posology adaptation (*after min 1 week*)
- ☐ Extra-pulmonary localization
- ☐ Other:

Sampling on heparinized tube kept on ice

Minimal approach (*For non-hospitalized patient or non-suffering of impaired absorption*)

- ☐ 5221 Isoniazid C2h
- ☐ 5222 Ethambutol C2h
- ☐ 5223 Pyrazinamide C2h
- ☐ 5224 Rifampicin C2h
- ☐ 5225 Rifabutin C3h
- ☐ 5226 Moxifloxacin C2h
- ☐ 5227 Levofloxacin C2h
- ☐ 52280 Linezolid C0
- ☐ 5229 Bedaquiline C0
- ☐ 52257 Rifabutin C7h

AREA UNDER THE CURVE (AUC) – Recommended approach

Sampling time : 0, 2h, 4h and 6h

- ☐ 52219 Isoniazide
- ☐ 52229 Ethambutol
- ☐ 52239 Pyrazinamide
- ☐ 52249 Rifampicin
- ☐ 52269 Moxifloxacin
- ☐ 52279 Levofloxacin

Posology	Isoniazid	Ethambutol	Pyrazinamide
Daily dosage	mg/kg	mg/kg	mg/kg
Posology	Rifampicin	Moxifloxacin	Levofloxacin
Daily dosage	mg/kg	mg/day + co-medication with Rifampicin: YES – NO	mg/day

TABLE TO FULLFILL FOR AUC APPROACH

Temps	0h	Time of drugs intake	2h	4h	6h
Theoretical hour					
Sampling hour					

