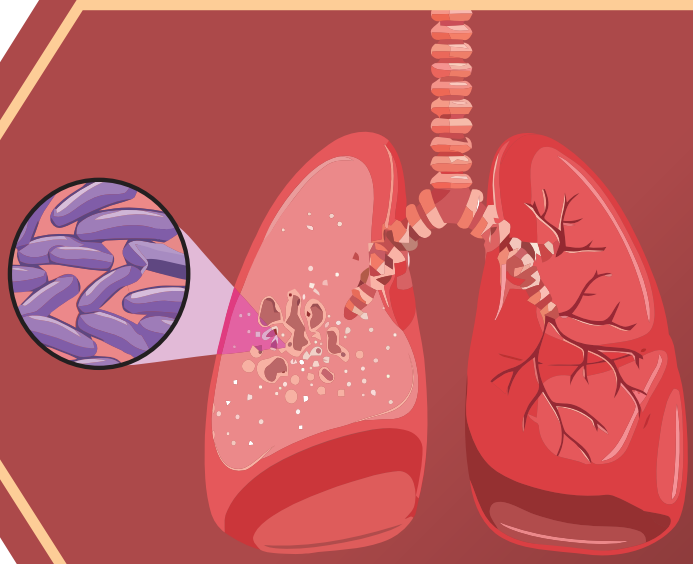
REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

Updated Clinical Guidelines for the Treatment and Programmatic Management of Drug Resistant Tuberculosis. Lebanon - 2021



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MINISTRY OF PUBLIC HEALTH
NATIONAL TUBERCULOSIS PROGRAM

Updated clinical guidelines for treatment and programmatic management of drug resistant tuberculosis, Lebanon - 2021

Abdul Rahman Bizri *(MD)* **-** ***Walid Alam*** *(MD)*
Alissar Rady *(MD)* **-** ***Hiam Yaacoub*** *(MD)*

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This version is dedicated to our colleagues medical doctors, health care workers, and patients.

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National Tuberculosis Program Manager

Dr. Hiam Yaacoub

Introduction

Tuberculosis (TB) is a bacterial disease with person to person transmission through the airborne route[1].

Mycobacteria are small rod-shaped bacilli that can cause a variety of diseases in humans.

They can be thought of in three main groups[2,3]:

- Mycobacterium tuberculosis complex: this group includes M. tuberculosis, M. bovis, M. africanum, M. microti, and M. canetti. They all can cause "tuberculosis" in humans. The vast majority of tuberculosis is caused by M. tuberculosis, with the other organisms being relatively rare.
- Mycobacterium leprae causes leprosy.
- Nontuberculous mycobacteria (NTM): this group includes all the other mycobacteria that can cause diseases in humans. NTM sometimes can cause clinical manifestations (in the lungs, skin, bones, or lymph nodes) similar to those of tuberculosis. Most NTM exist in the environment, are not usually spread from person to person and are often non-pathogenic in persons with intact immune system or healthy lung tissue.

All mycobacteria are classical acid-fast organisms and are named so because of the stains used in evaluation of tissue or sputum specimens (i.e. Ziehl-Neelsen stain,).

M. tuberculosis multiplies more slowly than most bacteria; this is why tuberculosis has a slower evolution (causes disease weeks or even months to years after infection) than most other bacterial infections[4].

M. tuberculosis is a strictly aerobic bacterium. It therefore multiplies better in pulmonary tissue (at the apex, where oxygen concentration is higher) than in the deeper organs.

TB mainly targets the lungs (pulmonary TB), but it can also affect other parts of the body (extra-pulmonary TB), especially the kidneys, brain, lymph nodes, or spine[5]. TB is a treatable and curable entity, but death can occur if proper and timely treatment is not given[6].

The emergence of drug-resistant TB (DR-TB) can complicate treatment. DR-TB can occur when the drugs used to treat TB are misused or mismanaged[7].

Examples of misuse or mismanagement include:

- Incomplete course of treatment
- Wrong treatment (duration, dosage, or combination)
- Unavailability of some drugs needed for proper treatment
- Poor quality drugs (misfit drugs, poor storage, …)

DR-TB is more common in people who[8,9,10,11,12,13]:

- Do not take anti-TB drugs regularly (poor compliance)
- Are unable to afford the costs of treatment, a problem that is likely to become more common considering Lebanon's economic crisis and drug shortages problem.
- Lack access to proper healthcare (poverty, medication shortage, healthcare workers shortage, insufficient medical facilities capacity…)
- Are unable to seek proper treatment as to avoid missing workdays and consequently income loss
- Are economic migrants, as is the case in Lebanon which hosts many migrants and refugees who may face systemic barriers to financing and healthcare.
- Do not take all their drugs (combination therapy)
- Re-develop TB disease after treatment for TB
- Come from areas or population group where DR-TB is common
- Are exposed to an individual with known DR-TB
- Are part of marginalized or neglected population
- Have comorbid conditions (Diabetes mellitus, alcoholism, smoker, malabsorption…)
- Have HIV or other causes of severe immunosuppression

Types of DR-TB[14,15].

1. Rifampicin resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.
2. Isoniazid resistant tuberculosis (Hr-TB): confirmed rifampicin-susceptible and isoniazid-resistant TB in vitro
3. Multi-Drug Resistant TB (MDR-TB): resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs represent the first line therapy used in all patients with TB disease.
4. Extensively-Drug Resistant TB (XDR-TB): resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one additional drug from group A (Bedaquilin, Linezolid).
5. Pre-XDR-TB: resistance to isoniazid and rifampicin and at least one quinolone.

Prevention of DR-TB[16]

- Strengthen DOTS strategy to improve adherence to treatment
- Quick diagnosis and no delay in therapy (early detection and treatment)
- Monitor therapy and response to treatment
- Avoid exposure to known DR-TB patients in closed or crowded places such as hospitals, prisons, or homeless shelters
- Adequate infection control practices in hospital and other health-care settings
- Adequate management of comorbidities (HIV, alcoholism, DM, smoking)
- Offer a proper support system for mental health
- Implement proper socio-economic support as weak social support and protection limits access to TB services and leads to poor adherence to treatment.
- Implement proper immigration policies as weak policies and inability of health systems to cope with a large influx of migrants, limit access to quality health services and leads to poor living conditions among refugees and migrants.

The Burden of DR-TB[17]

- MDR-TD and XDR-TB are relatively uncommon in Lebanon. Treatment is usually more difficult, longer, more expensive, more toxic, and associated with higher rates of failure and death.
- A national action plan for combatting TB was launched in 2017 with five objectives in alignment with the WHO End TB Strategy. The NSP is designed for five years and describes five objectives which are in alignment with the WHO End TB Strategy[18].

- Objective 1: By 2021 further decrease the burden of TB to lessthan 10 cases/100 000 population by increasing the efforts for case detection and improve treatment outcomes through the existing health service network.
- Objective 2: By 2021 decrease by half the burden of TB among migrants and increase case finding activities to all refugee populations newly arrived in Lebanon
- Objective 3: Achieve and sustain accurate surveillance, monitoring and evaluation, adherence to SOPs and obtain better estimates of TB situation for a reliable measurement of progress.
- Objective 4: Increase coordination among all stakeholders involved in TB prevention care and control, public and private, including social support actors by organizing formal meetings with stakeholders.
- Objective 5: Raise TB awareness, decrease stigma through a plan for communication and social mobilization and promote research.

Abbreviations and Acronyms

* AE: adverse event
* AIDS: acquired immunodeficiency syndrome
* ARV: anti-retroviral therapy
* AST: aspartate aminotransferase
* ATS: American Thoracic Society
* CDC: Center for Disease Control and Prevention
* DOT: directly observed treatment
* DR-TB: drug resistant TB
* DSM: direct smear microscopy
* DST: drug susceptibility testing
* FDC: fixed-dose combination (medicines)
* FLD: first-line drugs
* HIV: human immunodeficiency virus
* (H)REZ: (isoniazid)–rifampicin–ethambutol–pyrazinamide
* Hr-TB: confirmed rifampicin-susceptible, isoniazid-resistant TB
* IDSA: Infectious Diseases Society of America
* MOPH: Ministry of Public Health
* LTBI: latent tuberculosis infection
* MDR-TB: multidrug-resistant tuberculosis
* MDR/RR-TB: multidrug/rifampicin-resistant tuberculosis
* MENA: Middle East and North Africa
* NTP: National TB Programme
* PK/PD: pharmacokinetics/pharmacodynamics
* PLWHIV: people living with HIV
* RCT: randomized controlled trial
* RR-TB: rifampicin-resistant TB
* SAE: serious adverse event
* SAT: self-administered treatment or unsupervised treatment
* SGOT: serum glutamic oxaloacetic transaminase
* TB: tuberculosis
* VOT: video observed treatment
* WHO: World Health Organization

Abbreviations of Anti-TB Agents

* Am: amikacin
* Amx-Clv: amoxicillin-clavulanate
* Bdq: bedaquiline
* Clz: clofazimine
* Cm: capreomycin
* Cs: cycloserine
* Dlm: delamanid
* E: ethambutol
* Eto: ethionamide
* FQ: Fluoroquinolone
* Hh: high dose isoniazid
* Imp-Cln: imipenem–cilastatin
* Imp: imipenem
* Km: kanamycin
* Lfx: levofloxacin
* Lzd: linezolid
* Mfx: moxifloxacin
* Mpm: meropenem
* Pa: Pretomanid
* PAS: p-aminosalicylic acid
* Pto: prothionamide
* R: rifampicin
* S: Streptomycin
* T: thioacetazone
* Trd: terizidone
* Z: pyrazinamide

Classification of anti-TB agents

A newer classification was released in 2016 by the WHO for MDR/RR-TB anti-TB drugs, focusing on three groups of agents: A,B,and C[19] (Table 1).

Table 1 : Second Line Drugs: Classification of new and repurposed drugs for MDR-TB as per WHO 2019 Guidelines

Drug Groups	Drug
Group A:	1) Levofloxacin OR moxofloxacin 2) Bedaquiline 3) Linezolid
Group B:	4) Clofazimine 5) Cycloserine OR terizidone
Group C:	6) Ethambutol 7) Delamanid 8) Pyrazinamide 9) Imipenem-cilastatin OR meropenem 10) Amikacin 11) Ethionamide OR prothionamide 12) P-aminosalicylic acid

Key definitions[19,20]

- NTP: National Tuberculosis Programme is a part of MOPH. The program is committed to fight TB in Lebanon through the development and implementation of strategies and workplans that serve this goal, monitoring and reporting incidence, providing treatment, observing therapy, managing cases and contacts, dispensing medications, testing for susceptibility/resistance profiles and coordinating with WHO,
- Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB.
- New case is defined as a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB medicines for less than 1 month.
- Previously treated refers to patients who have received 1 month or more of anti-TB medicines in the past.
- Clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed based on X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory

confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

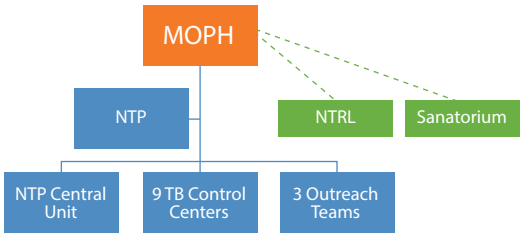
- Bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF).
- Drug-susceptibility testing (DST): refers to in-vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance-conferring mutations to a medicine
- Isoniazid-resistant TB (Hr-TB): refers to Mycobacterium tuberculosis strains in which resistance to isoniazid and susceptibility to rifampicin has been confirmed in vitro.
- Polyresistance refers to resistance to more than one first-line anti-TB drug, other than isoniazid and rifampicin together.
- Rifampicin-resistant TB (RR-TB) strains are considered not to be susceptible to rifampicin based on DST and, as a result, are eligible for treatment with MDR-TB regimens.
- Second-line TB medicine (or drug) is an agent reserved for the treatment of drug-resistant TB.
- Shorter MDR-TB regimen refers to a course of treatment for MDR/RR-TB lasting 9–12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings.
- Longer MDR-TB regimens: used for the treatment of MDR/RR-TB. They last 18 months or more and may be standardized or individualized. They are usually designed to include a minimum number of second-line TB medicines considered to be effective based on patient history or drug-resistance patterns.

Organization of TB prevention, care and control and NTP management in Lebanon

The National Tuberculosis Program (NTP) under the Ministry of Public Health (MoPH) of Lebanon operates through a central unit (NTP manager, epidemiologist and pharmacist) and 9 TB control centers across the country in addition to 3 outreach teams (field coordinators, DOT officers and community health volunteers). In June 2018, Laboratoire Rodolphe Merieux (LRM) was nominated by a decree through MoPH as the NTRL under Fondation Mérieux supervision. Furthermore, MoPH contracted a Sanatorium for the hospitalization and isolation of PTB and DR-TB cases many years ago. ***(Figure 1)***

Besides, two committees for Tuberculosis are available in the country; the TB national scientific committee (NTP manager, MDR TB focal point, NTRL representative, representatives of ID and Pulmonary societies….) and the TB national steering committee.

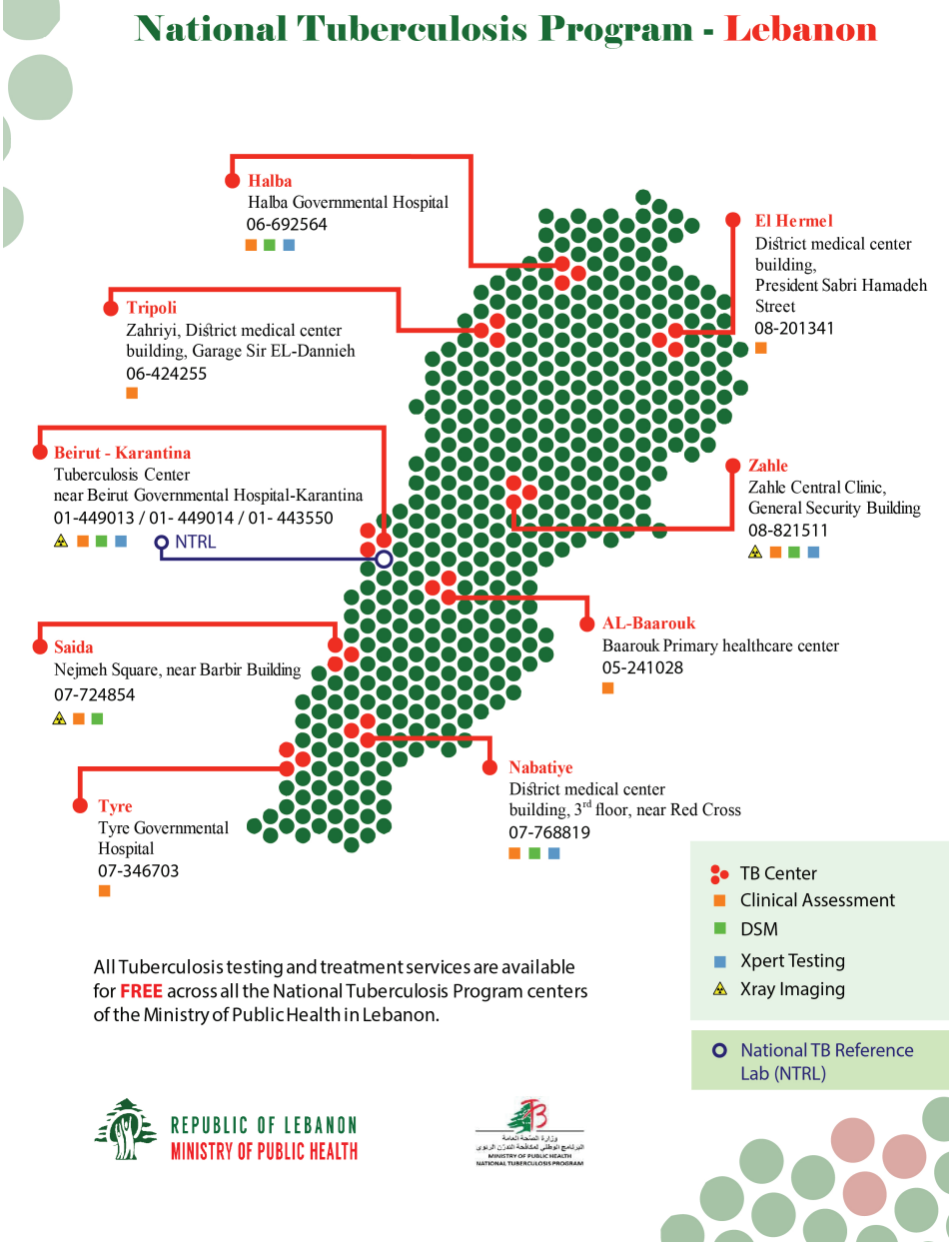
Figure 1: NTP Lebanon Organigram, 2020



The following services are available at the TB centers falling under the NTP and at NTRL:

- TB diagnostics and laboratory services (Chest Radiography, Direct smear microscopy and Xpert testing (available at the TB centers), Culture and DST for FLD and SLD (at NTRL-LRM) ***(Figure 2).***
- TB cases management and treatment for DS-TB and DR-TB.
- Treatment follow-up and support through DOT and VOT
- TB Contacts investigations and screening
- TB Prevention through the provision of preventive treatment for Latent TB cases in high risk groups when recommended (Migrants from TB HBC, TB Contacts, Immunocompromised patients…)

Figure 2: Geographical Distribution of NTP Centers and NTRL and Available Services, 2020



Tuberculosis Pharmacovigilance in Lebanon

Pharmacovigilance Implantation at National Level

- Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
- The Quality Assurance of Pharmaceutical Products (QAPP) Program, within the Lebanese Ministry of Public Health (MoPH), aims to reinforce the implementation of quality standards related to the safety of pharmaceutical products and to ensure that medicines and vaccines reach the patient in a safe, effective and acceptable manner.
- Lebanon joined the World Health Organization (WHO) Program for International Drug Monitoring (PIDM) through the QAPP Program who implemented the National Pharmacovigilance (PV) System at national level with the partnership of the Lebanese PV Center at the Faculty of Pharmacy/Lebanese University and in collaboration with the WHO Lebanon Office.
- The main activities in PV are detecting, reporting and assessing adverse events linked to medicines and vaccines
- The implementation of the national pharmacovigilance system that keeps track of any side effects caused by Drugs, will result in enhanced management of side effects.
- The occurrence of adverse events during second line anti-TB treatment can contribute to additional morbidity, treatment interruption, treatment failure, affect quality of life, or death. It is important that adverse drug reactions be routinely monitored for TB patients in treatment
- When introducing a new drug, a plan for implementing active PV is essential to record in a reliable way the evidence of adverse drug reactions or drug-drug interaction and use this information to inform decision makers, update clinical guidelines and treatment recommendations.
- NTP centers started to record side effects caused by the second line drugs using the quality management system on which the

health care professional or the pharmacist fill the adverse event reporting form for medicines & vaccines (which includes anonymous patient details, risk factors, products details, adverse event, outcome of adverse event, seriousness of adverse event, possible cause of adverse event).

- The NTP started reporting AE to the PV center as of November 2020.

Drug resistant tuberculosis in Lebanon

Published data is sparsely available regarding DR-TB in Lebanon. Information from the NTP suggest that the non-Lebanese population are major contributors to the incidence of DR-TB in Lebanon, albeit low as compared to other countries. Lebanon is the country with the highest number of refugees per capita in the world given the impact of the Syrian crisis, and the high number of foreign labors[21].

A 12-month nationwide study on the prevalence of DR-TB in Lebanon, conducted through a collaboration between the NTP and the Lebanese university, examined 720 cases of suspected TB in 2016-2017, confirmed 283 cases among them, and was able to test 250 patients. They were mainly Syrian, Lebanese, and Ethiopian, with the rest from other nations. Of the 250 patients, 3 had MDR-TB, and 3 had XDR-TB. 7 of the 250 patients had Rifampin resistance (RR-TB).

One Lebanese patient tested positive for MDR-TB, and one for XDR-TB. One Syrian was positive for XDR-TB, and one for MDR-TB. One Sudanese tested positive for XDR-TB, and two Ethiopians were MDR-TB positive . Of the 18 patients that were previously treated for TB, 2 were MDR-TB and 2 were XDR-TB, with one INH resistant. Of the 228 new TB cases, 1 was MDR-TB, 1 was XDR-TB, and 15 were INH resistant[22].

We recommend close monitoring of Syrian refugee population and foreign labor residential areas since they are the major contributors to the incidence of TB in Lebanon in general, and an important factor in the emergence of DR-TB. A recent study done in Lebanon showed a high percentage of resistance to fluoroquinolones not associated with MDR-TB[23].

Epidemiology of drug resistant tuberculosis in Lebanon

Lebanon is a low TB burden country with an estimated total and DR-TB incidence rates of 13 and 0.3 per 100000 populations respectively (WHO Global Tuberculosis Report 2020).

A total of 95 DR-TB cases have been notified between 2005 and 2020 in Lebanon, the majority having PTB (around 90%) and 56% being males. No DR-TB cases among pediatrics have been reported during that period and 40% of the cases were aged between 15 and 24 years between 2015 and 2020.

Notification among migrants increased gradually from 2013 onwards with a peak in 2019, Overall, about half of the cases notified between 2005 and 2020 were Lebanese, however the notification pattern among Lebanese and refugees is unstable over the years. ***(Figure 3).***

2017 marked the diagnosis of 3 XDR-TB cases, which were the first cases of XDR-TB reported in the country. Between 2018 and 2020, 3 other XDR-TB cases were found and treated. All XDR patients were foreign-born, 4 were males and 2 were females.

Regarding treatment success rate, it was constantly above 65% during the past 15 years except for 2008 and 2017 where it was very low. In general, low success rates are attributed to the fact that non-Lebanese TB cases are leaving the country before treatment completion and the program isn't being able to retrieve their treatment outcomes ***(Figure 4).***

In fact, when treatment outcomes are disaggregated by population subgroups, we notice a high success rate among Lebanese in most of the years and a low rate among the migrant population ***(Figure 5).***

Figure 3: Trends of Drug Resistant-TB cases by Population Subgroups, 2005-2020

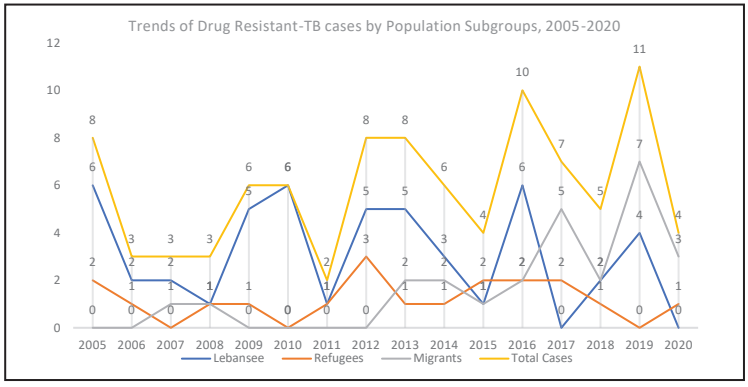


Figure 4: Trends in Success Rate of DR-TB Cases, 2005-2018

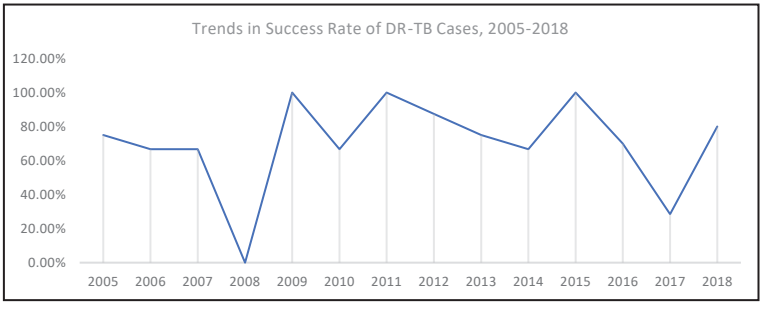
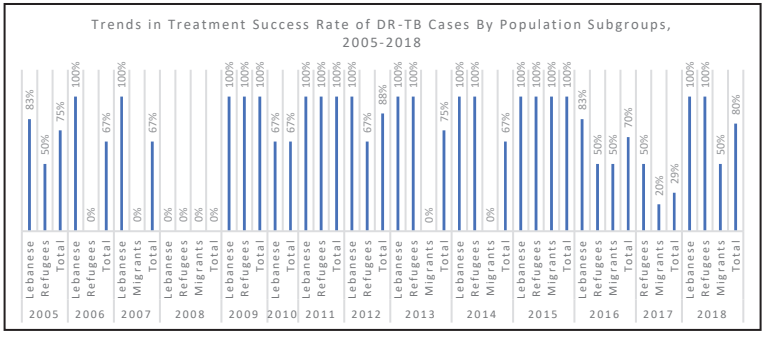


Figure 5: Trends in Success Rate of DR-TB Cases by Population Subgroups, 2005-2018



Executive summary

MDR-TB strains are harder to treat than drug-susceptible isolates. The increase in number of MDR-TB bacteria jeopardizes WHO's "End TB Strategy" set targets to eliminate the global TB epidemic[24]. It is important to establish evidence based clinical treatment and diagnosis guidelines that can be applied in all countries and settings. In accordance with this concept, the WHO consolidated guidelines on drug-resistant tuberculosis treatment fulfills the mandate of WHO to inform health professionals in Member States on how to improve treatment and care for patients with DR-TB[19].

In Lebanon the LMPH and the NTP with the support of the WHO have issued the "Lebanese Clinical Guidelines for the Treatment and Diagnosis of Tuberculosis" in 2017[25]. They included several sections about the treatment of DR-TB. Given the recent advances in management of MDR-TB and XDR-TB and the availability of newer drugs, several recent guidelines were established reflecting the position of the CDC, ATS, IDSA, European organizations and other key players. Moreover, several countries in the MENA region have already issued new guidelines for the treatment of DR-TB based on the local epidemiology and availability of anti-TB medications and diagnostic capabilities.

The present updated Lebanese guidelines will present the Lebanese approach towards diagnosis and treatment of individuals affected by DR-TB. They are mainly based on WHO consolidated guidelines, European and America recommendations and guidelines and the local epidemiology. They include recommendations on treatment regimens for isoniazid-resistant TB (Hr-TB) and multidrug- and rifampicin-resistant (MDR/RR-TB), including longer and shorter regimens for MDR/RR-TB, culture monitoring of patients on treatment, the timing of ART in MDR/RR-TB patients infected with HIV, the use of surgery in patients receiving MDR-TB treatment, and optimal models of patient support and care.

The updated WHO recommendations on treatment and care for DR-TB

1- Regimens for isoniazid-resistant tuberculosis (Hr-TB)[26,27]:

a. In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. Note INH resistance can only be confirmed with LPA early in the treatment, but most cases of INH resistance are found after failure of patient to achieve negative smear at the end of second month of treatment or any time later during the treatment. This is important as after a couple of months, patient can become MDR-TB and treatment with Lvx-RZE will lead to treatment failure and possible FQ resistance.

If Hr-TB is confirmed before TB treatment is started, then 6(H)REZ-Lfx is started immediately. If DST results taken in the beginning show susceptibility to INH, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR.

If Hr-TB is discovered after the start of treatment with 2HREZ/4HR regimen, i.e., either patients had undiagnosed INH resistance at the start or developed INH resistance while on first-line treatment, then rapid molecular testing for RR must be done (or repeated). Once RR is excluded, a full 6-month course of (H)REZ-Lfx is given.

b. In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, there is no extra benefit from adding an injectable aminoglycoside to the above regimen.

c. In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, there is no need to extend the above-mentioned regimen more than 6 months.

2- Use of the standardized, shorter MDR-TB regimen[28,29] (Annex-4)

a. In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.

b. Recommended shorter MDR-TB regimen:

i. Intensive phase: Duration: 4-6 months - Composition: 4 second-line drugs

ii. Continuation phase Duration: 5 months - Composition: 2 second-line drugs

iii. Supported by selected first-line TB drugs

c. Regimen Composition: **(4-6 Am-Mfx/Lfx-Pto/Eto-Cfz-Z-H high-dose-E/5 Mfx/Lfx-Cfz-Z-E)**

i. Intensive phase: 4-6 Am-Mfx-Pto-Cfz-Z-Hhigh-dose-E

ii. Continuation phase : 5 Mfx-Cfz-Z-E

d. All oral bedaquiline based shorter regimen **(6 Bdq-Mfx/Lfx-Pto/E-to-Cfz-Z-H high-dose-E / 4-5 Mfx/Lfx-Cfz-Z-E)**

e. Shorter all-oral bedaquiline-containing regimen for MDR/RR-TB enrollment criteria:

- Quinolone resistance ruled out;
- without resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance/ high dose INH can be effective in case of mutation in inhA but not in katG)
- without exposure to previous treatment with second-line medicines (used in the regimen) for > 1 month (unless susceptibility to these medicines is confirmed);
- without extensive TB disease and no severe extrapulmonary TB;
- not pregnant;

- children 6 years old and above/limited by bedaquiline indication.

- Extensive TB disease -presence of bilateral cavitary disease, extensive parenchymal damage on chest radiography, or disseminated form (i.e. more than one organ affected)
- Severe EPTB –miliary TB or meningitis
- DST results:
  - Essential–rifampicin and quinolones
  - Important–isoniazid and ethionamide (based on inhAand katGmutations); bedaquiline, clofazimine

f. Under Operational Research

Modified all-oral shorter MDR-TB regimens, which are different-from the recommended all-oral bedaquiline-based shorter regimen should only be implemented under operational research conditions with, as a minimum:

- A study protocol, the protocol must include a 12-month post-end-of-treatment follow-up.
- A clinical treatment guide that includes a patient consent process.
- An approval by the national ethics review board or ministry of health.

3- Use of longer MDR-TB regimen

a. The composition of longer MDR-TB regimen[19]

i. MDR/RR-TB patients on longer regimen should be started on all three group A agents with at least one Group B agent to ensure that at least four effective TB agents are used, and three agents are included in the rest of the treatment after bedaquiline is stopped (usually after 6 months of use). If only one or two Group A agents are used, both Group B agents must be included in the regimen. Group C agents are added only if the treatment regimen cannot include enough Group A and B agents (Table 1).

b. Considerations for longer all oral regimens for MDR/RR-TB

- Quinolone resistance excluded
- Patient not eligible for the shorter regimen (according to shorter regimen criteria)
- Careful regimen design in case of use in pregnancy
- Children or adults
- DST : Essential–rifampicin and quinolones, Important–bedaquiline, linezolid, clofazimine, delamanid, pyrazinamide

c. Duration of treatment[19]

i. Intensive phase: duration of treatment of between 5 and 7 months after culture conversion if regimen contains amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients

ii. Total treatment: duration of treatment between 15 and 21 months after culture conversion

iii. In patients with pre–XDR-TB and XDRTB: total treatment duration usually between 15 and 24 months after culture conversion but can be extended according to the patient's response to therapy.

iv. Bedaquiline (B), pretomanid (Pa) and linezolid (L), (BPaL) regimen can be considered, with a recent study showing favorable outcomes among 90% of a sample of 98 patients which included XDR-TB and MDR-TB[30].

d. Duration of bedaquiline treatment [31]

i. Does not usually exceed 6 months, but can consider use in special cases of MDR-TB including those with additional drug resistance, if the regimen is unlikely to achieve cure or poses a risk of creating additional drug resistance

ii. Week 1–2: Bedaquiline 400 mg (4 tablets of 100 mg) daily (seven days per week).

iii. Week 3–24: Bedaquiline 200 mg (2 tablets of 100 mg), three times per week (with at least 48 hours between doses) for a total dose of 600 mg per week.

iv. Week 26 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only, as per WHO standard recommendations. Use of bedaquiline beyond 6 months (end TB observational study) was available but not possible to assess the impact on efficacy, due to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond six months.

Use of bedaquiline and delamanid concurrently (end TB observational study and DELIBERATE trial). Evidence was insufficient to make an assessment of the efficacy or effectiveness of the concurrent use of bedaquiline and delamanid. There were no additional safety concerns with regards to the concurrent use of bedaquiline and delamanid.
Observational study in South Africa on bedaquiline exposure during pregnancy showed that only low birth weight was associated with bedaquiline exposure in utero. It was not possible to conclusively ascribe this effect to bedaquiline, and more investigation is needed to explore this relationship. There were no significant differences in infant growth after birth (infants followed up until 1 year of age).

WHO recommendation of off-label use of bedaquiline and delamanid[32,33].

1- Approaching off-label use:

- All other valid therapeutic options need to be exhausted. Regimens need to be reviewed carefully if failing to ensure that its components are optimized and can overcome the emergence of further drug-resistance. Ensure compliance with all medications, the quality of the drugs, optimal dosing, and review interactions with other medications that could limit effectiveness of any drugs in the regimen.
- Before considering off-label use, consultation with experts in management of MDR-TB should be sought (e.g. national MDRTB committees or MDR-TB consilia).

- Inform patients of the potential risks and obtain proper informed consent
- Close patient monitoring for response to treatment and active drug safety monitoring and management (aDSM) are mandatory. Detailed data should be collected about each treatment experience to inform both local and global policies.

2- Situations that might benefit from off-label use:

- Extrapulmonary TB: WHO guidelines accommodate the use of bedaquiline and delamanid in extrapulmonary forms of TB based on extrapolation of results from pulmonary TB; however, efficacy of both medicines remains unclear in extrapulmonary TB, especially in serious forms such as meningitis.
- Limited regimen options: Some patients may have extensive drug resistance or have drug intolerance or experience serious adverse effects that prevents the use of at least five effective medicines in a longer MDR regimen. Regimens of last resort in such patients may thus have to contain fewer effective medicines and should be used under prevailing ethical standards.
- Prolonged treatment: Use of these drugs beyond six months may be considered if the regimen is unlikely to achieve cure or poses a risk creating additional drug resistance
- Need for concomitant use: not regarded as off-label use and should be reserved for regimens of last resort in patients with extensive patterns of drug resistance, drug intolerance or serious adverse effects. Should be used under prevailing ethical standards. A 2019 study showed the combination to be relatively safe, with a reassuring cardiotoxicity profile and few adverse events, with a treatment success rate of 46%.

- Combination should not be used in children or pregnant women. Use of delamanid in children above 3 years of age has been recommended by WHO, and Bedaquilin above 6 years of age.

Table 2 Longer course MDR-TB regimen

Drug Groups	Drug
Group A: **All three drugs should be included**	- Levofloxacin OR moxofloxacin - Bedaquiline - Linezolid
Group B: **Add one or both drugs**	- Clofazimine - Cycloserine OR terizidone
Group C: **Add to complete the regimen and when drugs from Groups A and B**	- Ethambutol - Delamanid - Pyrazinamide - Imipenem-cilastatin OR meropenem - Amikacin - Ethionamide OR prothionamide - P-aminosalicylic acid

Post-exposure prophylaxis of Contacts Exposed to MDR-TB:

For contacts with presumed MDR LTBI due to exposure to an infectious patient with MDR-TB, treatment for LTBI is 6 to 12 months with a later-generation fluoroquinolone (levofloxacin or moxifloxacin) alone or with a second drug, based on drug susceptibility of the source-case M. tuberculosis isolate. Avoid pyrazinamide as a second drug due to toxicity, potential discontinuation, and potential resistance[34].

Treatment of MDR-TB in Special Situations (special host)

HIV infected individuals with DR-TB:

The management of MDR-TB is more complex among patients with HIV infection. The higher pill burden of combined ART with expanded TB drug therapy, potential drug–drug interactions, the management of immune reconstitution inflammatory syndrome (IRIS), and other concurrent HIV-associated opportunistic diseases all pose unique challenges in the care of these patients[35]. Reports from several countries suggest that there is an association between MDR-TB and HIV, as rifampin resistance has been identified more frequently in patients affected with both HIV and TB compared with those not infected with HIV[36]. Data from Lebanon does not necessarily suggest a similar pattern. Patients with MDR-TB and HIV have higher risk of mortality compared with those with MDR-TB without HIV. Low CD4 cell counts correlates with further increase in risk of mortality[37].

In HIV patients receiving therapy for drug-susceptible TB, significantly lower mortality was observed among patients receiving concurrent ART versus those not receiving ART[38]. In non-CNS drug susceptible TB, ART should be started within 2 weeks of initiating anti-TB therapy in those with CD4 cell counts <50 cells/ml and by 8 to 12 weeks for patients with higher CD4 cell counts . HIV patients are vulnerable to opportunistic infections (OI) which include TB, coccidioidomycosis, pneumocystis jirovecii pneumonia (PCP), and candidiasis among several others. These OIs should be treated promptly[40]. Meanwhile in HIV patients with MDR-TB no clear data exists to suggest the best timing for initiation of ART[39]. However, the decrease in mortality in patients treated for MDR-TB who are concurrently receiving ART, mainly among those with CD4 <50 cells/ml, supports a similar ART management approach as recommended for drug susceptible TB.

MDR-TB of the CNS in patients with HIV presents additional challenges. TB meningitis with isoniazid-resistant TB, RR-TB, or MDR-TB can be associated with higher mortality compared to drug susceptible disease[41]. Initiating ART early in patients with TB is associated

syndrome, and this can be even more problematic in CNS disease[42]. One study found that immediately starting ART does not improve outcome in HIV-associated tuberculous meningitis and leads to more adverse effects compared to delaying ART by 8 weeks[43]; however, there is a paucity of data in patients with MDR-TB of the CNS. The optimal approach remains unclear and close clinical monitoring is advised.

DDI between certain anti-TB drugs and ARTs must be accounted for as well as the increased risk of toxicity[44]. Therefore, management of patients with HIV and MDR-TB can best be performed by the TB national scientific Committee.

Treatment of MDR-TB in Children

Cases of drug-resistant tuberculosis in children are under-diagnosed causing children with DR-TB to act as a reservoir from which future cases will develop. By ignoring childhood TB, efforts at epidemic TB control will ultimately fail[45]. Given that the bacterial burden in young children with TB is much smaller than the burden in most adults, most drug resistance in children is primary and occurs when the organism is inhaled, making further development of resistance while on therapy (secondary resistance) much less common in children[34]. Additionally, the paucibacillary nature of pediatric TB presents a challenge for microbiologic confirmation due to difficulty in obtaining suitable specimens and poor sensitivity of available bacteriological tests[46]. Drug susceptibility in cases that meet clinical definitions of TB disease (i.e., microbiologic confirmation is not available) can only be determined by linking the child to a specific source case for whom susceptibilities of the organism are known. This is feasible in low endemicity countries such as Lebanon but extremely difficult in high-endemic countries.

Several factors can influence the outcome of treatment for MDR- and XDR-TB in children. MDR- and XDR-TB studies dealing with the two age extremes of childhood are sparse. Little is known about the pharmacokinetics, safety, and tolerability of the drugs used to treat drug-resistant TB in neonates, infants, and toddlers[47]. Children

more prone to develop disseminated TB, including meningitis, a risk that is especially high in those less than 2 years of age. Drugs such as linezolid might be preferred over ethambutol and bedaquiline due to the decreased CSF penetration of ethambutol and the unknown bioavailability of bedaquiline[48,49,50].

TB in adolescents can be similar to that found either in adults or in young children. Historically, most studies have focused on children (<15 years) and adults (≥15 years) in tuberculosis control with little attention given to tuberculosis incidence, diagnosis, management, and outcomes among adolescents (aged 10–14 years) [51]. Additionally, adolescents are excluded from TB treatment trials and most of the oral drugs used to treat MDR and XDR-TB are not licensed for use in children. Whether to use pediatric formulations, if available, or crush tablets or put them in suspension is another limiting factor which creates more uncertainty regarding the pharmacokinetics and pharmacodynamics of these various preparations. It is also advisable to avoid, when possible, injectable drugs because they are less tolerated in children. Children tolerate oral TB medications better than adults, with fewer serious adverse events resulting in lesser breaks in therapy.

Treatment of MDR-TB in Pregnant Women

Untreated MDR-TB during pregnancy is associated with higher maternal morbidity, mortality, and increased risk of vertical transmission. Adverse fetal outcomes occur at a much higher risk and include spontaneous abortions, fetal growth restriction, oligohydramnios, preterm labor, and increased neonatal mortality[52,53]. The decrease in T-helper 1 (Th-1)/Th-2 ratio in pregnant women makes them more vulnerable to TB during pregnancy and in the postpartum period and especially prone to disseminated TB[54].

Significant information gaps exist in the literature on treatment of MDR-TB in pregnant women, including the effectiveness, safety, and tolerability of available treatment regimens, as well as timing and duration of second-line drugs, with most guidance on treatment coming from case reports and case series. Additionally, most

of the second-line drugs are pregnancy category C per the U.S. Food and Drug Administration (FDA), except for bedaquiline and meropenem, which are classified as category B[55]. Aminoglycosides and ethionamide should also be avoided when possible, as aminoglycosides are teratogenic and ethionamide can increase the risk of nausea and vomiting associated with pregnancy[55].

Optimally, the regimen for MDR-TB in pregnancy should consist of at least four second-line anti-TB drugs that are likely to be effective against the infecting strain, plus pyrazinamide. But as previously mentioned, most of the second line anti-TB agents are pregnancy class C (Table 3)[56]. In cases of severe disease with no available alternatives, aminoglycosides can be used with close monitoring but should be deferred until after 20 weeks of pregnancy[56,57] . Bedaquiline and delamanid are not recommended for use in pregnancy by the WHO due to lack of enough data regarding efficacy and safety in pregnant women[58].

Ultimately, there is not enough evidence to support a particular regimen for MDR-TB treatment in pregnancy.

A decision on the timing of treatment for drug-resistant TB and the choice of a DR-TB regimen during pregnancy should take into consideration the gestational age of the fetus, and should weigh the risks of the teratogenic effects of anti-TB treatment against the potential benefit to the mother[59]. However, given the risk of disseminated TB, the priority likely lies in treatment of TB regardless of pregnancy term to ensure safety of the mother and the safety of breastfeeding at the end of the pregnancy.

All women of childbearing age that are started on anti-TB medication should be offered individualized, long term and effective contraception given the toxic effects of these drugs on pregnant women and their fetuses[56].

We therefore recommend a multidisciplinary team to manage DR-TB cases in pregnant women. The team should include the obstetrician following the patient, and the scientific TB committee (infection disease specialist , pulmonologist, MDR TB focal point, NTP manager)

health care professional or the pharmacist fill the adverse event reporting form for medicines & vaccines (which includes anonymous patient details, risk factors, products details, adverse event, outcome of adverse event, seriousness of adverse event, possible cause of adverse event).

- The NTP started reporting AE to the PV center as of November 2020.

Table 3. FDA based classification of drugs used for MDR-TB treatment during pregnancy

Category B	Category C	Category D	Not FDA approved
Amoxicillin / clavulanate Meropenem Bedaquiline	Pyrazinamide Fluoroquinolones Capreomycin Ethionamide Cycloserine/terizidone High-dose isoniazid Clofazimine Linezolid Imipenem-cilastatin	Aminoglycosides	Delamanid

Surgery in MDR-TB:

The role of surgery in the management of tuberculosis has changed over time. Initially, it was one of the earliest therapeutic tools used in the treatment of tuberculosis. However, its role has been rendered to an adjunct to therapy for TB in general, and for DR-TB as well[60]. Potential indications for surgery include failure of anti-TB therapy, relapse post therapy, localized or extensive pulmonary TB, and clinical complications such as empyema[34]. Even though little data exist, both WHO and ATS recommend elective partial lung resection in patients with MDR-TB on treatment[19,34].

Complimentary surgery may be associated with higher probability of treatment success, but will increase the cost of treatment[34]. Additionally, surgery is associated with an important risk of morbidity and mortality. It is useful to reduce bacilli burden while simultaneously removing the sites of high concentrations of drug resistant bacilli and is therefore recommended at the early stages of disease management.

Delaying surgery and continuing ineffective chemotherapy may facilitate progression of disease, and further promote the development of drug resistance[61]. Adjunct surgery in the form of partial lung resection for patients with DR-TB should be considered only if appropriate conditions can be ensured and include good surgical facilities, trained and experienced surgeons, and a careful selection of candidates. Lebanon has the capacity to provide good facilities and has many experienced surgeons[19].

While it may be needed for diagnosis, surgery may have a minor role in the management of extrapulmonary TB. It is reserved for certain late and serious complications including constrictive pericarditis, neurological abnormalities from Pott's disease, hydrocephalus, and obstructive uropathy. Incision and drainage may be helpful in enlarged fluctuant lymph nodes that are about to drain spontaneously[62].

Diagnosis of DR-TB

WHO recommends several diagnostic techniques for detection of resistance of M. tuberculosis isolates. These techniques are divided into phenotypic methods and molecular (genotypic) methods[63].

DST determines whether a population of M. tuberculosis bacilli is susceptible to anti-TB agents.

The Xpert MTB/RIF is a fast nucleic acid amplification test that is endorsed by the WHO for the detection of the MTB complex and RIF resistance screening in suspected cases in both adults and children (Annex 1 and 2). It should be used as first line for diagnosis of DR-TB and is widely available in Lebanon[25]and at the NTP.

The Xpert MTB/RIF assay uses semi-quantitative nested real-time PCR to amplify a fragment containing the 81 bp hotspot region of the rpoB gene (codons 507–533) that is then hybridized to five molecular beacon probes[64]. It is not prone to cross-contamination and has a sensitivity and specificity for smear-positive samples of 100 and 99%, respectively, and for smear-negative samples of 67 and 99%, respectively, compared to the standard culture-based DST. It allows detection of RIF resistance in just 2 hours[64,65]. Moreover, MTB detection rate is increased by 23% with the use of Xpert MTB/RIF compared with smear microscopy[66].

However, silent mutations can lead to false positive results[67], while false-negative results can occur because of the impossibility to detect RIF-resistance mutations outside the hotspot region of the rpoB gene[68]. The Xpert MTB/XDR, a new assay developed to detect MDR and XDR-TB resistance, is currently under endorsement process by the WHO. This assay is intended as a reflex test to detect resistance to INH, FLQ, ETH and Second Line Injectable Drugs Drugs (SLID) on unprocessed sputum samples and concentrated sputum sediments which are positive for Mycobacterium tuberculosis. It can differentiate low versus high-level resistance to INH and FLQ as well as cross-resistance versus individual resistance to SLIDs Results are obtained under 90 minutes[69].

Another technique that can be used is line probe assays (LPAs) which are DNA–DNA hybridization assays that detect different mutations using different probes[70]. Different LPAs target different hotspot regions of drug-resistance. WHO recommends for the initial drug resistance screening of sputum smear-positive samples the use of GenoType MTBDRplus, GenoType MTBDRsl, and Nipro NTM+MDR-TB[71].

GenoType MTBDRplus VER2.0 detects both RIF and INH resistance by screening mutations in rpoB, katG, and the inhA promoter[64]. Sensitivity of GenoType MTBDRplus VER2.0 for MDR detection is between 83.3 and 96.4%, and specificity between 98.6 and 100%[64]

GenoType MTBDRsl VER1.0 and VER2.0 detect the MTB complex and its resistance to FQs, ethambutol, and aminoglycosides/cyclic peptides by analyzing the gyrA, gyrB, rrs, embB, and eis genes. It may be used as an initial test for patients with confirmed RR-TB or MDR-TB[64].

Nipro NTM+MDR-TB detects MDR-TB cases by targeting rpoB, katG, and inhA and also differentiates four important Mycobacterium species (MTB, M. avium, M. intracellulare, and M. kansasii). Nipro NTM+MDRTB has a sensitivity of 50 to 95%, and a specificity of 97-100% for MDR detection[64].

Phenotypic methods of detection involve culturing of M. tuberculosis in the presence of anti-TB drugs to detect resistance. DST is most accurate for rifampicin and isoniazid. Rifampicin resistance is a valid and reliable indicator/proxy of MDR-TB in high burden settings[72]. However,

culture method is time-consuming and takes up to 3–8 weeks to get results[73]. In Lebanon, several labs have phenotypic detection capabilities. The NTP has an association with a local national TB referral lab supported by Fondation Merieux and hosted by the Saint Joseph University.

Follow up and monitoring of treatment (Table 5)

- A key component of monitoring the progress of treatment is ***patient-centered directly observed therapy (DOT).*** All treatment should be given under direct observation and DOT providers should be trained on the signs of treatment failure.

Table 4. Activities for monitoring treatment response[74]

MONITORING EVALUATION	***RECOMMENDED FREQUENCY***
Evaluation by clinician	During the intensive phase: Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable the patient is seen twice a month or once a month. During the continuation phase: Monthly assessments unless there is a medical necessity to see the patient more often.
Treatment adherence and tolerance	Regularly by the DOT provider.
Sputum smears and culture	Monitoring smears and culture monthly throughout treatment. (Note: programs with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)
Weight	At baseline, then every two weeks for first three months and then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four.
Chest radiograph	At baseline, and then every six months.

Common adverse events of anti-TB medications (Table 6)

Table 5. Remarks and serious adverse events (SAE) median risk for drugs used in longer regimen for MDR-TB[19]

Drugs	serious Adverse events (Median %) [sae]	remarks[75,76,77,78,79,80,81,82,83,84,85,86,87,88]
Bedaquiline	2.4	Monitor for QTc prolongation*, GI effects, rarely sensorineural toxicity
moxifloxacin	2.9	Monitor for QTc prolongation (high incidence), GI side effects, rarely CNS disorders†. Has a shorter half life
levofloxacin	4.1	Monitor for GI, rarely CNS side effects†
Linezolid	17.2	Monitor for lactic acidosis (especially seen with use for more than 28 days), anemia and thrombocytopenia, peripheral neuropathy, and *irreversible* optic neuropathy
clofazimine	3.6	Skin discoloration, ichthyosis and gastrointestinal adverse events
Cycloserine **terizidone**	7.8	Cycloserine: GI side effects, frequentneurological and psychiatric effects‡. Terizidone: Fewer than cycloserine; CNS effects†. > 1 g per day associated with hepatotoxicity, congestive heart failure, convulsions, and coma.
Ethambutol	4.0	Ocular toxicity, GI disturbances
Amikacin	10.3	Ototoxicity, nephrotoxicity
Pyrazinamide	8.8	Hepatotoxicity, hyperuricemia, sideroblastic anemia
Delamanid	Not enough data	Monitor QTc§.
meropenem	Not enough data	GI disturbances and dermatological manifestations**
Imipenem-cilastatin	Not enough data	GI disturbances, CNS effects†, dermatological manifestations**

* Perform ECG before starting bedaquiline and at least at weeks 2, 4 and every following month.
Discontinue if QTc > 500 ms.
† Headache, dizziness, tremors, epilepsy
‡ Anxiety, confusion, depression, psychosis, aggression, irritability, and paranoia
§ Very limited data regarding harm; WHO recommends any adverse drug reaction attributed to delamanid be reported to the national pharmacovigilance center
*** Pruritus, rash

Summary of good practices for patients evaluated and treated for DR-TB:

1. Should consult with the TB national scientific committee,
2. Molecular DSTs should be obtained for rapid detection of mutations associated with resistance. When rifampin resistance is detected, additional DST should be performed immediately for first-line drugs, fluoroquinolones, and bedaquiline and linezolid. Resistance to fluoroquinolones should be excluded whenever isoniazid resistance is found. To note INH resistance is either detected early with LPA or after conversion failure after 2 months in which case MDR-TB might develop. Once rifampicin resistance is excluded, a full 6-month course of (H)REZ-Lfx is given.
3. Regimens should include only drugs to which the patient's M. tuberculosis isolate has documented or high likelihood of susceptibility.
4. Response to treatment should be monitored clinically, radiographically, and bacteriologically. Cultures should be repeated at least monthly for pulmonary TB. If cultures remain positive following 3 months of treatment, susceptibility testing should be repeated. Signs of clinical response such as weight and other measures have to be recorded monthly.
5. AEs should be monitored and managed on every visit which should be at least monthly. Patients need to be educated about potential AEs and encouraged to report them.
6. Patient-centered case management should be applied, and patients encouraged to participate in their treatment decisions.
7. A multidisciplinary approach (TB committee, gynecologists, pediatrician…) is needed for special population mainly those with HIV, who are pregnant, and children.

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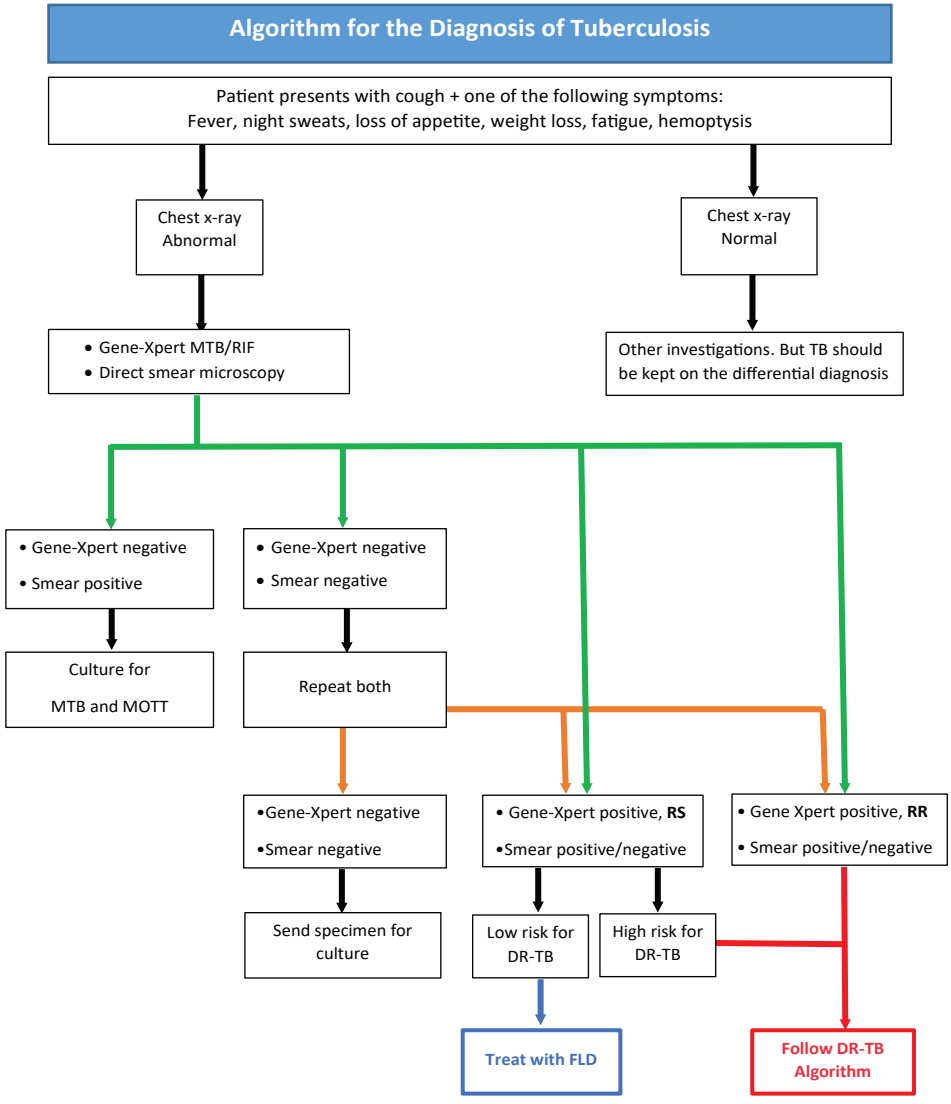
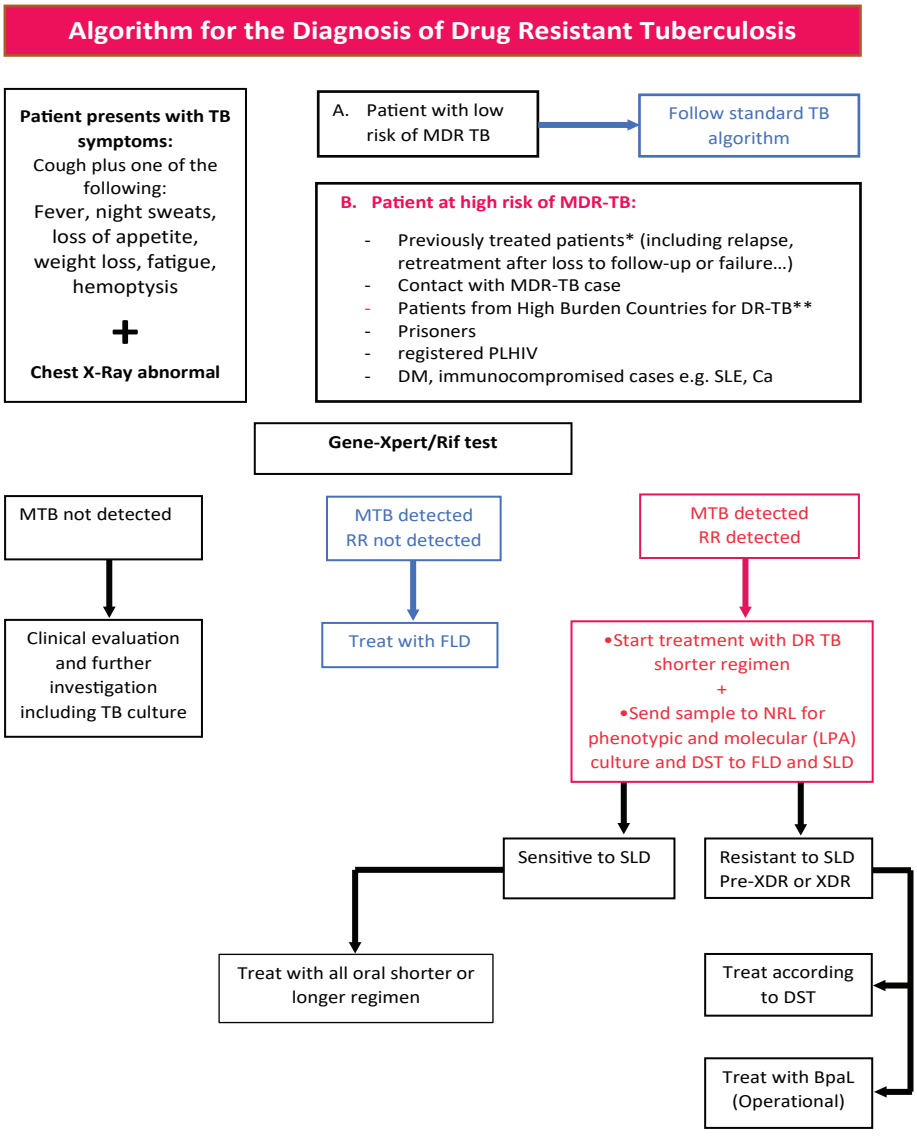
Annex1: Algorithm for the Diagnosis of TB



- For children suspected of having TB, diagnosis should be based on Xpert MTB/Rif and Culture
- For cases suspected of having EPTB, diagnosis should be based on Culture; Refer to Annex 3 "SOPs for Sample collection, handling and transportation to the National TB Reference Laboratory"
- Routine HIV counseling and testing should be offered to all TB patients

Annex2: Algorithm for the Daignosis of DR-TB



* a) Relapse: those who were previously treated and declared cured/ treatment completed and are now diagnosed with a recurrent episode of TB; b) Treatment after failure: those whose treatment failed (culture positive at 2 months of treatment or any time after 2 months of treatment; c) Treatment after loss to follow-up: those who have previously been treated and treatment was interrupted for more than 2 months.
** Refer to Annex 7 “WHO High Burden Country Lists for TB”

Annex3: Standard Operational Procedure for Laboratory (SOP: Pre-analytical requirement)

This SOP specifies the pre-analytical requirements to ensure a sample of high quality for mycobacteria testing. The quality and quantity of specimens collected, and the proper handling and transportation to the laboratory are critical to the successful isolation of mycobacteria.

I. General precautions and recommendations

1. Fill one request form for each specimen sent to the laboratory.
2. Separate the request form from the specimen container.
3. Respect the volume and type of container required for each sample.
4. Use sterile, leak proof, non-breakable, sealed containers.
5. Do not add formalin, preservative or fixative to the specimen.
6. Exclude EDTA, which greatly inhibits mycobacterial growth even in trace amounts.
7. Do not send the collected sample in a syringe.
8. Do not use swabs. Swabs are in general not optimal.
9. Avoid contamination by tap water or any other liquid that may contain living or non- living environmental mycobacteria and cause excessive errors.
10. Label clearly name of the patient, date of collection and center ID on the side of the container, not on the cap.
11. Refrigerate samples that cannot be transported within 2 hours to the referral laboratory to reduce growth of contaminating organism. Do not freeze the samples.
12. Check with the transporter the availability of a cold pack before shipping the samples.

All samples that do not meet the recommendations of this SOP, will not be processed.

II. Specimen collection

Specimen type	Sample Collection material	Volume Requirement
Sputum	Sterile Container	Minimum Volume 2 ml
BAL	Sterile Container	Minimum Volume 2 ml
Bronchial wash/brush	Sterile Container	Minimum Volume 2 ml
Transtracheal Aspirate Endotracheal Aspirate	Sterile Container	Minimum Volume 2 ml
Gastric Aspirate	Sterile Container	Minimum Volume 2 ml
Cerebral Spinal Fluid CSF	Sterile Container	Minimum Volume 1 ml
Other body fluids (pleural, pericardial, synovial, ascitic)	Sterile Container	Minimum Volume 2 ml
Tissues or Lymph Nodes biopsies	Sterile Container ***N.B.*** *No Formalin, no preservatives, no fixatives.* *If the specimen may dry, add a few drops of sterile saline water.*	1g of tissue, if possible
Pus	Sterile Container	Minimum Volume 2 ml
Urine : First morning specimen	Sterile container	Minimum Volume 2 ml

III. Specimen handling

Refrigerate samples at 2-8°C until ready for transport to the laboratory for 72 hours maximum.

Note: For urine specimens, refrigerate at 2-8°C until ready for transport to the laboratory for 24 hours maximum.

Annex4: Treatment Regimens for Drug Resistant Tuberculosis

1. Regimen for rifampicin susceptible and isoniazid resistant TB

* In patients with confirmed rifampicin-susceptible, isoniazid resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for duration of 6 months.

Hr-TB regimen: 6(H) REZ-Lfx

* If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H High dose) REZ may be prescribed daily for 6 months.

Hh	High-dose Isoniazid
R	Rifampicin
E	Ethambutol
Z	Pyrazinamide
Lfx	Levofloxacin

2. The shorter all-oral bedaquiline-containing regimen for MDR/RR-TB

* In patients with at least confirmed resistance to rifampicin, for whom resistance to fluoroquinolones has been ruled out.

The regimen can be summarized as: 4–6 Bdq(6 m) –Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E
Initial phase: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto
Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

* Bedaquiline(Bdq) is used for 6 months.
* Levofloxacin/moxifloxacin(Lfx/Mfx), ethionamide(Eto), ethambutol(E), isoniazid (high dose)(Hh), pyrazinamide(Z) and clofazimine(Cfz) are used for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear and/ or culture positive at the end of 4 months), followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide.

* In children below 6 years of age, bedaquiline is not yet recommended by WHO.
* The regimen contains ethionamide, which is usually contraindicated in pregnancy; longer regimens can be designed to avoid known toxicities.

4. The shorter injectable containing regimen

* If bedaquiline cannot be used or not available, amikacin (Amk) for 6 months may replace bedaquiline.
* The recommended regimen for MDR-TB with no resistance to second line is as follow:

4-6 Amk-Lfx/Mfx-Eto-Cfz-Z-Hh-E/5-6 Lfx/Mfx-Cfz-Z-E

5. Longer regimens for MDR/RR-TB (5-drugs regimen)

* MDR/RR-TB patients who are not eligible for shorter regimens, including those with quinolone resistance

18-20 Bdq(6 m)-Lfx/ Mfx-Lzd-Cfz-Cs

* Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.
* Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens
* Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used.
* P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used.
* Use of Lzd for at least 6 months was shown to increase effectiveness, although toxicity may limit its use.
* In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

6. Treatment Regimens – pre XDR & XDR TB

* Longer regimen design according to the DST results.
* A treatment regimen(BPaL) lasting 6–9 months, composed of bedaquiline(Bdq), pretomanid(Pa) and linezolid high dose (Lzd) may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones (pre XDR), who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks, or MDR TB +resistance to Quinoiones and one of the two other medicines from group A (XDR).

BPaL regimen: 6–9 Bdq- Pa-Lzd

* The BPaL regimen is given for duration of 6–9 months. The standard treatment duration is 6 months. If the sputum culture taken after 4 months of treatment is positive, patients can receive an additional 3 months of treatment (total 9 months)
* The dose of linezolid can be reduced from 1200 mg once daily to 600 mg or 300 mg once daily
* Children (0–13 years) and Pregnant and lactating women were excluded from the study

Annex 5: CHOOSING THE DR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply?

* Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (quinolones, injectable second line drugs…) (except isoniazid resistance)
* Exposure to one or more second-line medicines in the shorter MDR-TB regimen for >1 month
* Intolerance to one or more medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
* Pregnancy
* Extra pulmonary disease
* At least one medicine in the shorter MDR-TB regimen not available in the program

NO **YES**

Failing regimen or any exclusion criterion

Annex 6: Adverse Events of Drug Resistant TB Medications

Drug	Daily Doses	Serious Adverse Events*	Most Common Adverse Events	Monitoring	Contraindications	Cautions
Pretomanid	200 mg	– Peripheral Neuropathy – Transaminases elevation – GGT elevation – Hyperamylasemia – Visual impairment – Testicular atrophy – Hypoglycemia	– Acne – Anemia – Nausea & Vomiting – Musculoskeletal pain – Rash – Dyspepsia – Hemoptysis	CBC, ECG, ALT, AST, Bilirubin, electrolytes, Lipase, Amylase, Creatinine, Lactate, Blood glucose	In patient whom Bdq &/or Lzd are CI	Hepatic Adverse Reactions, Reproductive toxicities (under study)
Bedaquiline	1) Adult:Week 1-2: 400mg once daily Week 3-24: 200mg three times per week (at least 48hrs between doses) 2) Children (6-17 years): 6mg/kd/day for 14 days then 3-4 mg/kg thrice weakly.	– ECG QT prolongation – Transaminase elevation – Blood amylase elevation – Athralgia	– Nausea, – Headache – Chest pain – Anorexia – Rash	ECG, LFTs, Electrolytes, Bilirubin, lipase, amylase, lactate	Hypersensitivity, Children (<6years). Discontinue if : Aminotransferase increases are accompanied by total bilirubin elevation >2 x ULN Amino transferase >8 xULN Aminotransferase>5 x ULN persist beyond 2 weeks	QT prolongation, Alcohol uses, Renal disease.
Linezolid	1) Adults: 600mg or high dose 1200mg 2) Children: >16kg: 10-12 mg/kg/day <16kg:15mg/kg/day	– Abnormal LFTs – Lactic acidosis – Myelosuppression – Peripheral & optic Neuropathy – Serotonin syndrome	– Headache, – Diarrhea, – Nausea& Vomiting – Dizziness – Rash – Metallic taste – Tongue discoloration – Increased BUN – Fungal infection	CBC, Peripheral Neuropathy, Lactate, Liver enzyme, Color vision.	Hypersensitivity, Mono-amine oxidase inhibitors, Breast feeding.	Pregnancy, Epilepsy, Peripheral and Optic Neuropathy.
Cycloserine	1) Adults: 10-20 mg/kg/day, max 1gper day with or without food. 2) Children: 15-20 mg/kg/day in two divided dose. 3) If CrCL <30 ml/min 250 mg once daily or 500 mg three times aweek.	– Heart Failure – Seizure – Liver enzymes increased – Dysarthria – Cardiac arrhythmia – Anxiety – Depression – Confusion	– Dizziness – Rash – Photosensitivity – Vitamin b12 or folic acid deficiency	CBC, Renal function, Electrolytes, ECG, Liver enzyme, Psychosocial counseling, liver enzyme	Hypersensitivity, Severe anxiety, Depression, Alcohol dependence, Severe renal impairment.	Pregnancy, Breast feeding, Central nervous system toxicity, Renal disease, Allergic dermatitis.

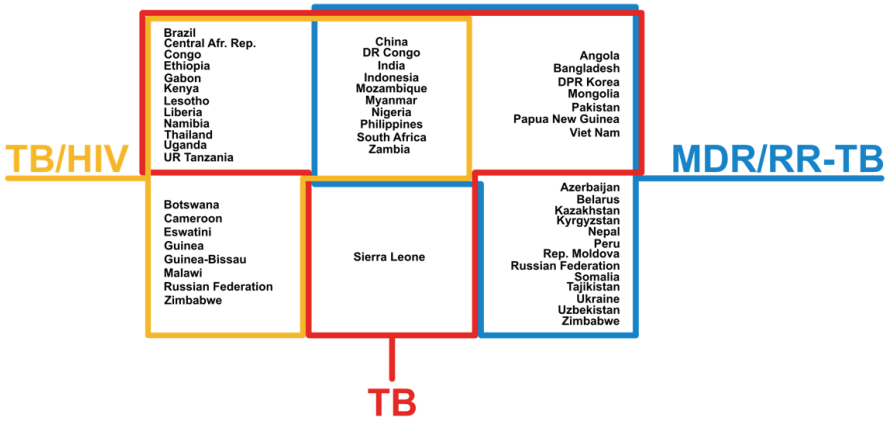
***** Adverse event that might lead to death, permanent or significant disability, prolongation of hospitalization, congenital anomaly.

Delamanid	1) Adults: 100mg twice a day for 24 weeks with food. 2) Children: ○ 3-5 years: 25 mg PO bid ○ 6-11 years : 50 mg PO bid ○ 12-17 years: 100 mg PO bid	– QTc prolongation – Increase LFTs – Hypokalemia – Anxiety – Depression	– Dermatitis – Urticarial – Nausea & Vomiting – Diarrhea – Insomnia – Tremor – Anemia – Tinnitus – Hypercholesterolemia – Joint pain	ECG, Electrolytes, Albumin.	Hypersensitivity, Serum albumin <2.8 g/dl, Taking medicinal products that are strong inducers of CYP3A4 (Carbamazepine), Pregnancy, Breast feeding, children <3 years	Alcohol misuse, QT prolongation
Amikacin	1) Adults: 15- 20mg/kg/day	– Nephrotoxicity – Ototoxicity – Neurotoxicity – Hypotension	– Hypocalcaemia – Hypomagnesaemia – Hypokalemia	Renal function, Auditory, Electrolytes.	Hypersensitivity, Myasthenia gravis,	Obese, Elderly, Renal Disease.

	(up to 1g) 2) Children: 15-20 mg/kg/day 3) If CrCl <30 ml/min : 12-15 mg/kg three times per week				Pregnancy.	
Levofloxacin	1) Adults : 10-15 mg/kg/day (up to 1000mg once daily) with or without food 2) Children: <5 years : 7.5- 10 mg/kg twice a day 3) >5 years : 10-15mg/kg once daily 4) If CrCl <30 ml/min: 750 – 1000 mg three times per week.	– QTc prolongation – Hypoglycemia – Hyperglycemia – Arthralgia – Increased hepatic enzymes – Anxiety – Thrombocytopenia – seizure	– Nausea – Headache – Diarrhea – Insomnia – Constipation – Dizziness – Dyspepsia – Rash – Edema – Tendon rupture	ECG (baseline, 2 weeks, & every 3 months), LFTs, CBC, Blood glucose.	Hypersensitivity, Tendon damage.	Myasthenia Gravis, Long QT syndrome, Renal disease.
Moxifloxacin	1) Adults: weight < 30kg: 400mg once a day. Weight 30-50 kg : 600 mg once a day. Weight >50 kg: 800 mg once a day with	– Prolonged QT interval – Increase LFTs – Acute renal failure – Seizure – Thrombocytopenia – Hepatitis – Hypoglycemia	– Headache – Dizziness – Nausea – Diarrhea – Decreased amylase – Increase serum chloride – Anemia – Hypokalemia – Photosensitivity – Tendon rupture	ECG, LFTs, CBC, Blood Glucose, amylase, calcium	Hypersensitivity, Tendon damage.	Sunlight, Myasthenia gravis, Liver disease, Peripheral neuropathy.

	or without food. Children: 7.5- 10 mg/kg once a day If CrCl <30 ml/min: 400 mg daily.					
Ethionamide	Adults: 15-20 mg/kg /day (up to 1 g) with or without food Children: 15-20 mg/kg/day If CrCl < 30 ml/min : 250-500mg / day	– Thrombocytopenia – Elevated Liver transaminases – Hepatitis – Optic neuritis – Peripheral neuropathy – Depression – Hypoglycemia – Hypothyroidism	– Stomach discomfort – Excessive salivation – Nausea, Vomiting – Diarrhea – Rash – Feeling of pins and needles – Anorexia – Metallic taste	Blood glucose, TSH/T4, LFTs.	Hypersensitivity, Severe liver disease, Pregnancy, Porphyria.	Renal disease, Breast feeding.
P-amino salicylate sodium (PAS)	1) Adults: 150 mg/kg/day in two to four divided dose (up to 12 g) 2) Children: 200- 300 mg/kg/day into 2 daily doses	– Hypothyroidism – Acute Hepatitis – Hemolytic anemia – Thrombocytopenia	– Nausea, Vomiting – Diarrhea – Abdominal pain – Jaundice – Crystalluria – Rash	TSH/T4, Liver function, Electrolytes.	Hypersensitivity, Renal disease.	Pregnancy, Breast feeding.
Clofazimine	Adults: 100 mg daily with meals Children: 2-5 mg/kg/day	– Phototoxicity – GI bleeding – Depression – Elevated levels of albumin, serum bilirubin, SGOT – Hypokalemia – Maculopathy – Increased blood glucose & ESR	– Pink to brownish-black skin discoloration – Nausea, Vomiting – Diarrhea – Abdominal pain – Rash – Dry skin – Pruritus – Conjuctival pigmentation – Discoloration of urine, feces, sputum & sweat	ECG, CBC, Blood glucose, Electrolytes.	Hypersensitivity to Clofazimine & to Peanuts or Soya.	Pregnancy, Breast feeding, QT prolongation, Liver disease, GI problems.

Annex 7: High Burden Country Lists for TB by WHO



The three global HBC lists for TB, TB/HIV and MDR/RR-TB by WHO 2021–2025.

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