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Clinical management of drug-resistant tuberculosis: A comprehensive review

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Abstract

Drug-resistant tuberculosis (DR-TB) continues to pose a serious challenge to global health. Forms such as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are much harder to treat, often requiring longer therapy with lower success rates compared to standard TB. This review outlines the clinical management of DR-TB, covering its spread, classification, underlying mechanisms, and treatment approaches. Resistance in *Mycobacterium tuberculosis* mainly develops due to natural genetic changes, which are worsened by improper treatment practices like incomplete therapy and poor adherence. These conditions allow resistant bacteria to survive and spread. Although there has been a slight global decline in MDR-TB cases, the burden remains high, especially in certain countries. Recent advancements, including newer drugs like bedaquiline and delamanid, have improved treatment outcomes and made shorter, all-oral regimens possible. Effective management requires careful drug selection, patient monitoring, and strong adherence support. Following WHO and national guidelines is essential to improve success rates. Managing DR-TB requires early detection, proper treatment strategies, and patient-focused care. Continued research and better access to newer therapies will be key in controlling this disease.

Keywords: Drug-resistant tuberculosis, MDR-TB, XDR-TB, *Mycobacterium tuberculosis*, TREATMENT strategies

1. Introduction

Tuberculosis, or TB, is a massive global health problem that just won't go away. It is caused by a persistent bacterium called *Mycobacterium tuberculosis*. Even with our modern medicine, it remains one of the top infectious killers on the planet. Every year, roughly 10.6 million people get sick with TB, and about 1.6 million lose their lives to it. While the number of cases is slowly dropping, the progress is frustratingly sluggish, proving that our current control strategies still have major holes.

1.1 The rise of Drug Resistance

One of the biggest hurdles today is the spread of drug-resistant tuberculosis (DR-TB). This has turned a difficult situation into a genuine global crisis. We usually categorize these resistant strains into two main types:

1.2 Multidrug-Resistant TB (MDR-TB)

This is when the bacteria can survive isoniazid and rifampicin. These are our two strongest first-line weapons. There are about 450,000 new cases of MDR-TB every single year.

1.3 Extensively Drug-Resistant TB (XDR-TB)

This is even scarier. It resists the first-line drugs plus fluoroquinolones and at least one injectable second-line drug. Because so many medicines fail against it, the chances of a full recovery are much lower.

1.4 Why is it spreading?

The data shows that drug resistance isn't just growing; it's getting more complicated. In countries hit hardest by the disease, about 3.6% of new patients have MDR-TB. However,

for people who have been treated for TB in the past, that number jumps to over 20%. So, how does this happen? Usually, it starts with a genetic mutation in the bacteria. This becomes a problem when patients don't finish their full course of medicine or when the drugs provided are low-quality or incorrect. Once a resistant strain develops, it can spread from person to person just like regular TB. This turns a personal medical failure into a community-wide epidemic.

1.5 The Struggle of Treatment

Treating drug-resistant TB is a marathon, not a sprint. While "regular" TB can often be cured in six months, DR-TB treatment can drag on for 9 to 24 months.

The drugs used are often:

- Less effective than standard treatments.
- More toxic, leading to severe side effects.
- Extremely expensive, putting a massive strain on healthcare budgets.

Because the treatment is so long and painful, many patients find it hard to stick with it. This is why the success rate for DR-TB is only about 50-60%, which is a far cry from the 85% success rate we see with drug-sensitive cases.

1.6 Reasons for Hope

It's not all bad news, though. We've seen some incredible breakthroughs recently. New rapid molecular tests can now identify resistant strains in hours instead of weeks. We also have new drugs like bedaquiline, delamanid, and pretomanid. These are game-changers because they allow for shorter, all-oral treatment plans. No more painful daily injections for two years.

Because TB is constantly evolving, we have to stay ahead of it. Understanding how to manage these resistant cases is vital for doctors and public health officials. This review takes a deep dive into how we diagnose the disease today, the best ways to treat it, and the hurdles we still need to clear to finally get TB under control.

2. The global landscape of drug-resistant TB

According to the latest 2025 Global Tuberculosis Report from the World Health Organization (WHO), we have been tracking drug resistance trends since 1994. The primary focus of this surveillance is on MDR/RR-TB. This category combines two types of resistance: Rifampicin-resistant TB (RR-TB) and Multidrug-resistant TB (MDR-TB), which is specifically resistant to both rifampicin and isoniazid. These two medications are the heavy hitters of first-line TB treatment, so when they fail, the challenge grows significantly.

Fortunately, our ability to estimate and track these cases has improved. The data shows a hopeful trend: the global burden of MDR/RR-TB has been slowly but steadily dropping since 2015. By 2024, estimates suggest that roughly 390,000 people developed these resistant forms of the disease (Tan *et al.*, 2025; Ye *et al.*, 2025) ^[16, 23]. While this progress is encouraging, there is still a major blind spot, many countries lack the advanced surveillance systems needed to track resistance to other types of anti-TB drugs.

2.1 Where is the burden highest?

The distribution of drug-resistant TB is not uniform across the globe. In fact, in 2024, more than half of all MDR/RR-TB cases were found in just four countries (Figure-01):

- India: Carries the heaviest burden by far, accounting for roughly 32% of all global cases.
- China: Represents about 7.1% of the total.
- The Philippines: Also accounts for approximately 7.1%.
- Russian Federation: Contributes about 6.7%.

Because such a massive portion of the crisis is concentrated in these specific regions, global health efforts must prioritize supporting these healthcare systems to turn the tide against the epidemic (Prasad *et al.*, 2017; Tan *et al.*, 2025; Vedi *et al.*, 2025) ^[11, 16, 21].

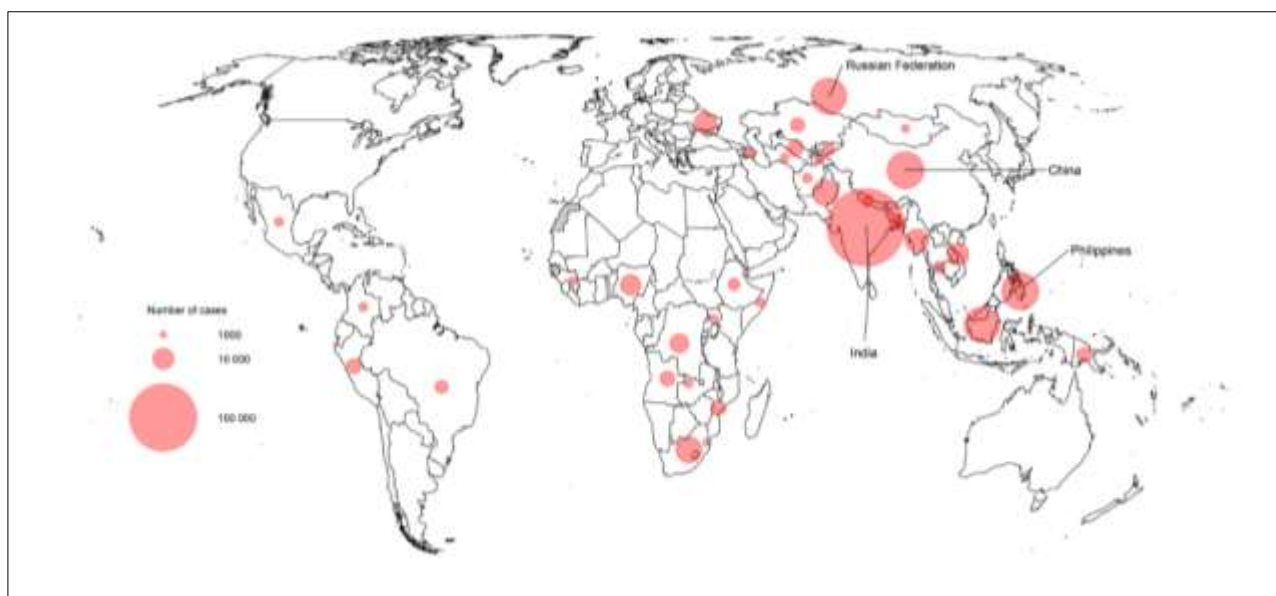


Fig 1: Estimated number of people who developed MDR/RR-TB (incident cases) in 2024, for countries with at least 1000 incident cases

3. Classification of drug-resistant tuberculosis

To effectively treatment of TB, doctors have to know exactly which drugs the bacteria can ignore. We categorize

drug-resistant TB (DR-TB) based on how many and which medications no longer work. This classification is vital for picking the right treatment plan and understanding a

patient's chances of recovery (Raj *et al.*, 2024; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-a)^[12].

3.1 How we classify drug resistance

The different levels of resistance are like a ladder, getting more dangerous as we move up:

- **Mono-resistant TB:** The bacteria are resistant to just one of the first-line drugs (like isoniazid or rifampicin), but the others still work perfectly.
- **Poly-resistant TB:** The bacteria can resist two or more first-line drugs, but crucially, not both isoniazid and rifampicin at the same time.
- **Multidrug-resistant TB (MDR-TB):** This is a major turning point. The bacteria resist at least both isoniazid and rifampicin. Since these are our "heavy hitters," the disease becomes much harder to treat.
- **Pre-extensively drug-resistant TB (Pre-XDR TB):** This is MDR-TB plus resistance to one more specific group either fluoroquinolones or second-line injectables, but not both.
- **Extensively drug-resistant TB (XDR-TB):** This is the most dangerous level. It is MDR-TB that also resists both fluoroquinolones and at least one second-line injectable drug. Options for treatment are very limited here.

4. Rationale for the development of drug-resistant tuberculosis

Drug resistance in tuberculosis primarily develops due to the natural ability of *Mycobacterium tuberculosis* to undergo spontaneous genetic mutations. These mutations occur slowly but continuously during bacterial replication. As a result, a small proportion of the bacterial population may become resistant even before exposure to anti-tubercular drugs (Guenauoui *et al.*, 2016; *Holistic Health and Antimicrobial Resistance: A Zoonotic Perspective*, n.d.; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-a; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-b; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-c; Tan *et al.*, 2025)^[2, 16]. This is a natural biological phenomenon and differs for each drug. There are three main factors leading to amplification of resistance as shown in table-01.

Table 1: Factors leading to amplification of resistance

S/N	Factor	Effect
1	Incomplete treatment	Allows survival of resistant bacteria
2	Incorrect dosing	Reduces drug effectiveness
3	Poor adherence	Promotes selection of resistant strains

The frequency of spontaneous resistance varies depending on the drug used. For example, resistance to isoniazid and streptomycin occurs approximately in 1 out of every 10⁶ bacterial cell divisions, while rifampicin resistance is much less frequent, occurring in about 1 out of 10⁹ divisions. In contrast, resistance to ethambutol and pyrazinamide occurs more commonly, at a rate of approximately 1 in 10⁵ cell divisions (Table-02)

Although these mutations arise naturally, improper treatment plays a major role in selecting and amplifying resistant strains. When anti-TB drugs are used incorrectly such as in incomplete regimens, or poor adherence, the susceptible bacteria are eliminated, while resistant mutants survive and multiply. Over time, this leads to the development and dominance of drug-resistant tuberculosis. Some of these mutations just happen to make the bacteria immune to a specific drug. The rate at which this happens depends on the drug:

Table 2: Mutation frequency associated with resistance to first-line anti-tuberculosis drugs

S/N	Drug	Frequency of Resistance
1	Isoniazid	1 in 10 ⁶ cell divisions
2	Rifampicin	1 in 10 ⁹ cell divisions
3	Streptomycin	1 in 10 ⁶ cell divisions
4	Ethambutol	1 in 10 ⁵ cell divisions
5	Pyrazinamide	1 in 10 ⁵ cell divisions

5. Pathogenesis and Mechanisms of drug resistance

Anti-tuberculosis drugs are usually divided into two groups: older drugs and newer drugs. It is important to understand how these medicines work and how resistance develops. This helps doctors choose the right treatment for tuberculosis. Drug resistance in tuberculosis mainly happens because of natural genetic changes in *Mycobacterium tuberculosis*. These changes occur on their own when the bacteria multiply, even if no drugs are used. To better understand how different drugs act and how resistance develops against them, the table (Table-03) below summarizes the mechanisms of action and resistance patterns of selected anti-tuberculosis drugs (Guenauoui *et al.*, 2016; Murudkar *et al.*, 2015; Prasad *et al.*, n.d.)^[2, 8, 11].

Table 3: Mechanism of action and resistance of selected anti-TB drugs

Drug	Mechanism of action	Mechanism of resistance
Isoniazid (INH)	Prodrug activated by KatG; inhibits mycolic acid synthesis	Mutations in <i>katG</i> or <i>inhA</i> genes
Macrolides (Clarithromycin)	Binds 50S ribosomal subunit; inhibits protein synthesis	Low permeability + <i>erm(37)</i> gene expression
Ethionamide	Prodrug activated by EthA; inhibits mycolic acid synthesis (InhA target)	Mutations in <i>ethA</i> , <i>inhA</i> , or mycothiol pathway
Capreomycin	Inhibits protein synthesis via 16S rRNA	Mutations in <i>rrs</i> gene
Cycloserine	Inhibits cell wall synthesis (AlrA & Ddl enzymes)	Overexpression of target enzymes (AlrA, Ddl)
Para-aminosalicylic acid (PAS)	Inhibits folic acid synthesis	Mutations in <i>thyA</i> gene
Fluoroquinolones	Inhibit DNA gyrase	Mutations in <i>gyrA</i> and <i>gyrB</i> genes

Problems begin when treatment is not followed properly. This can happen if the patient stops medicine early, takes the wrong dose, or misses doses. In such cases, the normal bacteria are killed, but the resistant ones survive. These resistant bacteria then grow and become dominant. Over

time, this leads to drug-resistant TB. These resistant bacteria can also spread from one person to another. This makes the disease harder to control (Murudkar *et al.*, 2015)^[8]. So, both natural mutations and improper treatment contribute to the development and spread of drug resistance

in tuberculosis. This process is further illustrated in Figure-02, Mechanisms and Pathways of Drug-Resistant Tuberculosis Development and Transmission, which

provides a visual overview of how resistance emerges and spreads within populations.

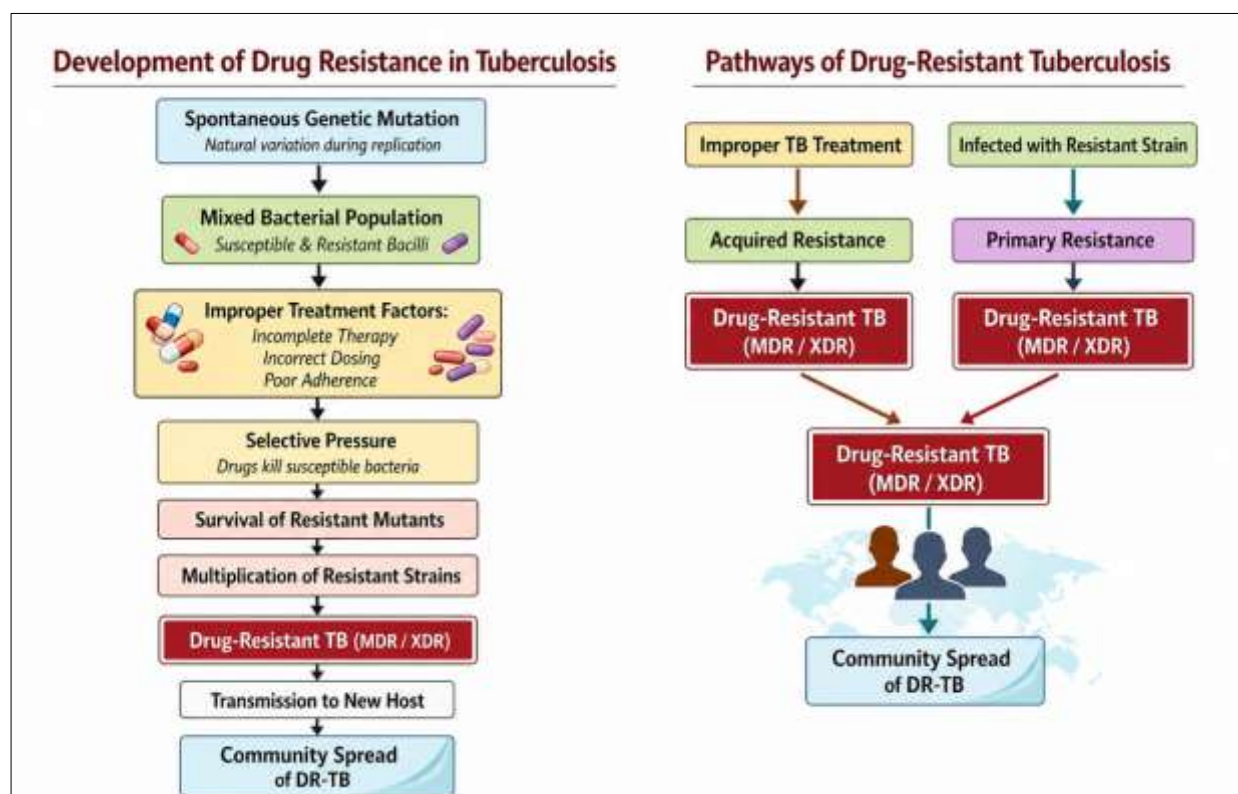


Fig 2: Mechanisms and pathways of drug-resistant tuberculosis development and transmission.

6. Role of improper treatment in MDR

Improper treatment plays a central role in the development of drug-resistant tuberculosis. Although spontaneous genetic mutations occur naturally in *Mycobacterium tuberculosis*, resistance becomes clinically significant when treatment is not given correctly. Factors such as incomplete therapy, incorrect dosing, and poor patient adherence allow some bacteria to survive despite drug exposure. These surviving bacteria are often the resistant mutants, which then multiply and become dominant (Kumar *et al.*, 2018; Tan *et al.*, 2025; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-a) [6, 16].

In addition, the use of poor-quality drugs or irregular drug supply can further reduce treatment effectiveness. Over time, this selective pressure leads to the emergence of multidrug-resistant and extensively drug-resistant TB. Moreover, these resistant strains can spread from one person to another, making improper treatment not only an individual problem but also a public health concern. To further clarify the biological basis of resistance development, Table 04: Spontaneous Mutation Rates and Development of Drug Resistance in Tuberculosis presents key aspects related to mutation and the emergence of resistant bacterial populations.

Table 4: Spontaneous mutation rates and development of drug resistance in tuberculosis

S/N	Aspect	Description
1	Basis of Resistance	Spontaneous genetic mutations in <i>Mycobacterium tuberculosis</i> during replication
2	Nature of Mutation	Occurs naturally, slowly, and continuously without drug exposure
3	Initial Population	Small proportion of bacteria may already be resistant before treatment

7. Novel Anti-Tuberculosis Drugs

In the last few years, several new anti-tuberculosis drugs have been developed. This progress has been especially important for treating drug-resistant forms such as MDR-TB. These newer agents work in ways that are different from conventional drugs. Because of this, they provide additional options when standard treatments fail or become less effective.

Nitroimidazoles, such as PA-824 and delamanid, are considered prodrugs. They become active inside the bacteria, particularly under low-oxygen conditions. This is important because *Mycobacterium tuberculosis* can survive in such environments within the human body. Once

activated, these drugs generate reactive molecules. These molecules are capable of killing both actively dividing bacteria and dormant forms. Resistance to nitroimidazoles mainly develops due to mutations in genes involved in drug activation. When activation is impaired, the drug loses its effectiveness (Dookie *et al.*, 2022; Husain *et al.*, 2021; Prasad *et al.*, 2017; Vedi *et al.*, 2025) [1, 4, 11, 21].

Bedaquiline is another important addition to modern TB therapy. It targets ATP synthase, an enzyme that plays a key role in energy production in *M. tuberculosis*. By disrupting energy generation, the drug effectively weakens and kills the bacteria. Resistance to bedaquiline is often associated with mutations in the *atpE* gene. However, other resistance

mechanisms have also been suggested and are still being studied.

Oxazolidinones, such as linezolid, act by inhibiting protein synthesis. They bind to the 50S ribosomal subunit of the bacterial ribosome. This prevents the bacteria from producing essential proteins required for survival and growth. Resistance to oxazolidinones usually arises due to mutations in the 23S rRNA gene. These mutations reduce the binding ability of the drug, making treatment less effective (Jain *et al.*, 2024; Kumari *et al.*, 2025; Vedi *et al.*, 2025) [5, 7, 21].

SQ109 is another promising compound that has shown potential in improving TB treatment outcomes. It is believed to interfere with cell wall processes and membrane transport mechanisms. This drug may also enhance the activity of other anti-TB drugs. It has shown effectiveness against MDR-TB strains as well. However, its exact resistance mechanisms are not yet fully understood, and further research is ongoing.

Phenothiazines, such as thioridazine, have also demonstrated activity against *M. tuberculosis*. They are effective against both drug-sensitive and drug-resistant strains. Their action involves interference with bacterial enzymes and efflux pumps. By inhibiting efflux pumps, these drugs can increase the intracellular concentration of antibiotics, thereby improving treatment efficacy.

Benzothiazinones (BTZs) represent another important class of new anti-TB agents. These drugs act by inhibiting enzymes involved in cell wall synthesis. The mycobacterial cell wall is essential for bacterial survival and protection. When its synthesis is disrupted, the bacteria cannot maintain structural integrity and eventually die. This targeted mechanism makes BTZs a promising option for future TB therapies (Dookie *et al.*, 2022; Kumari *et al.*, 2025; Raj *et al.*, 2024) [1, 7, 12].

8. Management strategies for MDR/XDR-TB

The management of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is much more challenging than treating drug-susceptible TB. In these cases, the most effective first-line drugs, such as isoniazid and rifampicin, no longer work. Because of this, treatment depends on second-line drugs. These drugs are usually less powerful and often have more side effects. As a result, patients need longer treatment courses, and multiple drugs must be used together to achieve successful outcomes. A key principle in managing MDR/XDR-TB is to use any first-line drug that still remains effective against the organism. Even partial susceptibility can be useful when designing a treatment regimen. This helps in strengthening the overall effectiveness of therapy.

During the intensive phase of treatment, an injectable agent is commonly included. This drug is continued for a minimum of six months after culture conversion, which means after the patient's sputum tests become negative for the bacteria. Injectable drugs play an important role in reducing bacterial load during the early phase of treatment.

Fluoroquinolones are considered one of the most important components of MDR/XDR-TB treatment. Whenever possible, they should be included in the regimen because of their strong activity against *Mycobacterium tuberculosis*. Their use significantly improves treatment outcomes.

In addition to these, other second-line drugs are added to the regimen. The goal is to ensure that at least four to five drugs

in the combination are effective against the bacteria. Using multiple active drugs reduces the chances of further resistance developing and increases the likelihood of treatment success.

In patients with severe disease, such as those with extensive lung damage or advanced stages of infection, treatment becomes even more demanding. Similarly, cases with high-level drug resistance require stronger and more carefully designed regimens. In such situations, additional drugs with proven antimycobacterial activity may be included. These added agents help in strengthening the treatment plan and improving the chances of recovery.

9. Guidelines for the management of MDR-TB

National tuberculosis control programs have developed clear and structured guidelines to manage multidrug-resistant tuberculosis (MDR-TB). These guidelines are designed to ensure that patients receive effective and standardized care. Proper management is not simple. It requires trained healthcare professionals, reliable diagnostic facilities, and well-defined treatment protocols.

Ideally, MDR-TB cases should be managed in specialized centers. These centers are equipped with experienced clinicians and proper laboratory support. Such a setup helps in accurate diagnosis, careful monitoring, and better handling of complications. Diagnosis of MDR-TB is usually based on a combination of factors. These include a history of previous TB treatment, possible exposure to drug-resistant cases, and laboratory confirmation. Culture tests and Drug Susceptibility Testing (DST) carried out in quality-assured laboratories play a key role in confirming resistance.

However, interpreting DST results is not always straightforward. There can be variability in test results, especially for some first-line and second-line drugs. Because of this, results should be interpreted with caution and clinical judgment. Before starting treatment, each patient should undergo a detailed clinical evaluation. Baseline investigations are also important to assess overall health and to identify any risk factors.

Most national programs follow standardized treatment regimens. These are designed based on common resistance patterns and are easier to implement on a large scale. In some cases, individualized regimens may be required. This is especially true for patients with known resistance profiles or those who have received prior treatment. Treatment for MDR-TB is long and demanding. It usually includes an intensive phase of at least six months, which may be extended if needed. This is followed by a continuation phase that can last 18 months or even longer (Umashankar, 2019) [20].

Regular follow-up is a crucial part of treatment. Patients need periodic sputum examinations and culture tests to monitor response. Clinical assessment is also done throughout the treatment period to check for improvement or complications. Ensuring adherence to treatment is one of the most important factors for success. Methods such as directly observed treatment (DOT), proper patient counselling, and family support play a major role in helping patients complete their therapy (Kumar *et al.*, 2018; Rajput *et al.*, 2021; Sue Chie *et al.*, n.d.; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-c) [6, 13, 15].

Maintaining proper records is equally important. Documentation helps track patient progress, monitor side effects, and evaluate final outcomes. It also supports better decision-making during the course of treatment.

The management of extensively drug-resistant TB (XDR-TB) follows similar principles but is more challenging. Treatment options are limited, so regimens need to be more individualized and often more aggressive. In selected patients, surgical intervention may be considered. Management of co-existing conditions, such as HIV infection, is also essential for better outcomes.

According to World Health Organization (WHO) recommendations, treatment regimens should include multiple effective second-line drugs. These often include fluoroquinolones, injectable agents, and other companion drugs. The exact combination should be tailored to the patient's resistance pattern. Careful drug selection, along with strict adherence to treatment guidelines, is necessary to improve treatment success and to prevent the development of further resistance (Tan *et al.*, 2025; TB EPIDEMIOLOGY MULTI-DRUG RESISTANT TB (MDR-TB) Prevalence of MDR-TB, n.d.-c)^[16].

10. Risk factors for drug-resistant tuberculosis

The development of drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), is influenced by a combination of clinical, microbiological, and socio-environmental factors. Identifying these risk factors is essential for early detection, prevention, and effective management of the disease.

10.1. Previous tuberculosis treatment

A history of prior anti-tuberculosis therapy is one of the most significant risk factors for DR-TB. Inadequate or incomplete treatment, improper drug regimens, and treatment default can lead to the survival of resistant bacilli. Re-treatment cases, especially those with repeated treatment failure, have a higher likelihood of developing MDR-TB.

10.2. Poor treatment adherence

Non-adherence to prescribed treatment regimens plays a major role in the emergence of drug resistance. Irregular drug intake, early discontinuation of therapy, and lack of proper supervision allow partially resistant bacteria to survive and multiply, eventually leading to resistant strains.

10.3. HIV co-infection

HIV infection significantly increases the risk of developing drug-resistant TB. Immunocompromised individuals are more susceptible to infection and re-infection with resistant strains. In addition, drug interactions between antiretroviral therapy and anti-TB drugs may complicate treatment and contribute to resistance.

10.4. Contact with drug-resistant TB Cases

Close contact with individuals infected with MDR-TB or XDR-TB increases the risk of acquiring resistant strains directly. This highlights the importance of infection control measures, especially in household and healthcare settings.

10.5. Geographic and migration factors

People living in or migrating from regions with a high prevalence of MDR-TB are at increased risk. Cross-border

transmission and population movement contribute to the global spread of resistant TB.

10.6. Socioeconomic factors

Poverty, overcrowding, malnutrition, and limited access to healthcare services significantly contribute to the burden of DR-TB. These conditions not only increase transmission but also affect treatment adherence and outcomes.

10.7. Institutional exposure

Settings such as prisons, shelters, and hospitals with poor infection control practices facilitate the rapid spread of drug-resistant TB. Overcrowding and delayed diagnosis further increase the risk.

10.8. Programmatic and treatment errors

Errors in TB management, such as improper prescription of drugs, use of inadequate regimens, poor-quality medicines, and lack of proper monitoring, are major contributors to resistance. Weak healthcare systems and poor implementation of TB control programs further worsen the situation.

10.9. Other factors promoting resistance development

Certain biological and treatment-related factors can enhance the development of resistance, including:

- Malabsorption of drugs, leading to suboptimal drug levels
- Drug intolerance, resulting in interrupted or incomplete therapy
- Drug interactions, reducing the effectiveness of anti-TB medications

11. XDR-TB

Extensively drug-resistant tuberculosis (XDR-TB) represents one of the most serious and difficult-to-treat forms of drug-resistant TB. It is defined as multidrug-resistant TB (MDR-TB) that shows additional resistance to fluoroquinolones and at least one second-line injectable drug. This combination of resistance significantly limits treatment options and makes disease management more complicated.

At the global level, it is estimated that nearly 9% of MDR-TB cases eventually progress to XDR-TB. In India, various studies have reported a slightly lower prevalence, generally ranging between 3% and 4% among MDR-TB patients. Although the percentage may appear small, the clinical impact is substantial due to limited therapeutic choices and poorer treatment outcomes.

The development of XDR-TB is not due to a single factor. Instead, it results from a combination of patient-related, treatment-related, social, and exposure-related factors that together contribute to the emergence and spread of highly resistant strains.

To better understand these contributing factors, Table 05: Factors Associated with the Development of XDR-TB presents a categorized overview:

11.1 Patient-related factors

Include poor adherence to treatment and co-existing conditions such as HIV infection. These conditions can weaken the immune response and reduce treatment effectiveness.

11.2 Treatment-related factors

It involves improper drug regimens and incomplete therapy. When treatment is not correctly designed or not completed, it creates conditions that allow resistant bacteria to survive and multiply.

11.3 Social factors

such as poverty and overcrowding play a major role in both disease transmission and treatment challenges. Limited access to healthcare and poor living conditions can increase the risk of infection and hinder proper treatment.

11.4 Exposure-related factors

It include direct contact with individuals who already have MDR-TB. Such exposure increases the likelihood of acquiring resistant strains from the beginning.

Understanding these interconnected factors is essential for designing effective prevention and control strategies, as well as improving treatment outcomes in patients with XDR-TB.

Table 5: Factors associated with the development of XDR-TB

Category	Examples
Patient-related	Poor adherence, HIV infection
Treatment-related	Improper regimen, incomplete therapy
Social factors	Poverty, overcrowding
Exposure-related	Contact with MDR-TB cases

12. Diagnosis of Drug-Resistant Tuberculosis

Early and accurate diagnosis of drug-resistant tuberculosis (DR-TB) is essential for timely initiation of appropriate treatment and for preventing further transmission. Diagnostic approaches can be broadly classified into conventional methods and rapid molecular techniques.

12.1 Conventional methods (Culture and Drug Susceptibility Testing - DST)

Conventional diagnosis relies on culture of *Mycobacterium tuberculosis* followed by drug susceptibility testing (DST). Culture can be performed on solid media (e.g., Löwenstein-Jensen) or liquid systems (e.g., MGIT), which are considered the gold standard. DST helps determine

resistance to first-line and second-line drugs, allowing individualized treatment. However, these methods are time-consuming, often requiring several weeks, and need well-equipped laboratory facilities.

12.2 Molecular diagnostics (GeneXpert and Line Probe Assay - LPA)

Molecular techniques have revolutionized the diagnosis of DR-TB by providing rapid and accurate results. The GeneXpert (CBNAAT) test can detect *M. tuberculosis* and rifampicin resistance within a few hours, making it highly useful for early diagnosis. Line Probe Assays (LPA) identify genetic mutations associated with resistance to isoniazid, rifampicin, and some second-line drugs. These methods are faster than culture-based techniques and are increasingly used in high-burden settings.

12.3 Challenges in diagnosis

Despite advancements, several challenges remain in diagnosing DR-TB. Limited access to advanced diagnostic tools in resource-poor settings leads to underdiagnosis and delayed treatment. Conventional methods are slow, while molecular tests may not detect all resistance patterns. In addition, laboratory infrastructure, trained personnel, and cost constraints can affect the widespread implementation of these diagnostic techniques.

To provide a clear comparison of these diagnostic approaches, Table 06: Common Diagnostic Methods for Drug-Resistant Tuberculosis summarizes their advantages and limitations (Prasad *et al.*, 2017) ^[11].

Table 6: Common diagnostic methods for drug-resistant tuberculosis summarizes their advantages and limitations

S/N	Method	Advantages	Limitations
1	Culture & DST	Gold standard, detailed resistance profile	Time-consuming
2	GeneXpert	Rapid, detects rifampicin resistance	Limited resistance detection
3	LPA	Detects multiple gene mutations	Requires lab setup

13 Pharmacological treatment of drug-resistant tuberculosis

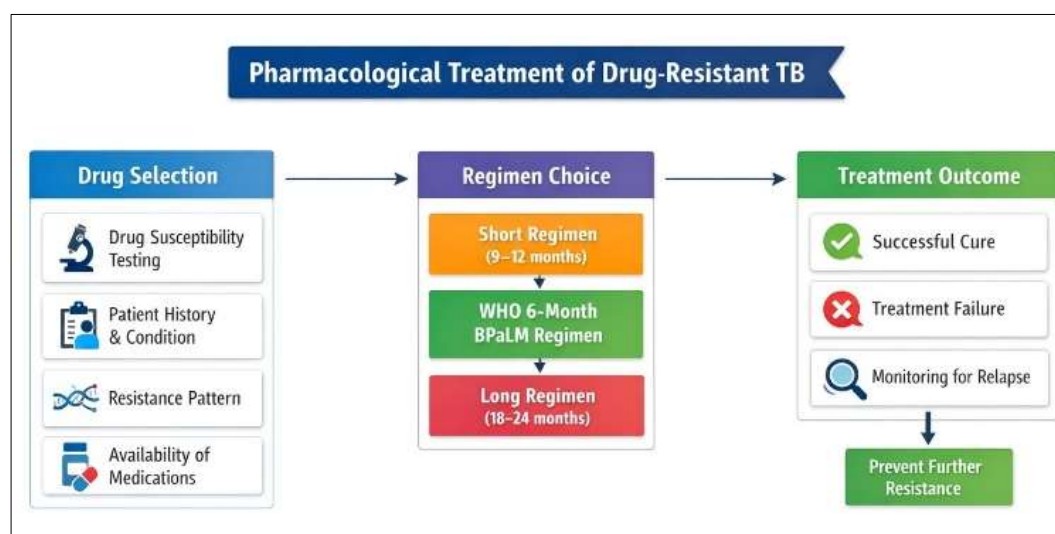


Fig 3: Pharmacological treatment pathway of drug-resistant tuberculosis

The pharmacological management of drug-resistant tuberculosis (DR-TB) is complex and requires the use of multiple drugs over a prolonged period. Treatment is guided by drug susceptibility patterns, patient history, and disease severity (Figure-03). The goal is to achieve cure while preventing further resistance.

13.1 First-line drugs (Brief Overview)

First-line anti-tuberculosis drugs include isoniazid, rifampicin, pyrazinamide, and ethambutol. These drugs are highly effective in drug-susceptible TB; however, in DR-TB, especially MDR-TB and XDR-TB, resistance to isoniazid and rifampicin limits their use. Some first-line drugs like pyrazinamide and ethambutol may still be included if susceptibility is confirmed.

13.2 Second-line drugs

Second-line drugs are the backbone of DR-TB treatment. These drugs are less potent, more toxic, and more expensive than first-line agents. They include:

- Fluoroquinolones (e.g., levofloxacin, moxifloxacin) - key components of most regimens
- Injectable agents (e.g., amikacin, kanamycin, capreomycin) - used mainly in intensive phase
- Oral second-line drugs (e.g., ethionamide, cycloserine, para-aminosalicylic acid)

Treatment regimens usually include at least 4-5 effective drugs to ensure adequate bacterial killing and prevent resistance amplification.

13.3 New and repurposed drugs

Recent advancements have introduced newer drugs that have significantly improved DR-TB treatment outcomes:

- Bedaquiline - inhibits ATP synthase, essential for bacterial energy production

- Delamanid - inhibits mycolic acid synthesis in the bacterial cell wall
- Pretomanid - active against both replicating and dormant bacilli

These drugs are now widely used in all-oral regimens and have reduced the need for injectable drugs.

13.4 Short vs Long treatment regimens

- Short Regimen (9-12 months): Used in selected patients with limited resistance. It is more convenient and improves adherence.
- Long Regimen (18-24 months or more): Required for patients with extensive resistance or complicated disease. It involves prolonged use of multiple second-line drugs.

13.5 WHO-Recommended Regimens

The World Health Organization (WHO) recommends all-oral regimens as the preferred approach for DR-TB management:

- 6-month BPaLM regimen (Bedaquiline + Pretomanid + Linezolid + Moxifloxacin)
→ Preferred for many MDR/RR-TB patients
- 9-month standardized regimen
→ Includes bedaquiline, fluoroquinolones, and companion drugs
- Long individualized regimen (≥18 months)
→ Used in XDR-TB or complex resistance patterns

Treatment selection depends on drug resistance profile, prior treatment history, and patient condition. To better understand the different drug groups used in therapy, Table 07: Drug Categories in DR-TB Treatment outlines key categories, their examples, and their roles in current treatment regimens.

Table 7: Drug Categories in DR-TB Treatment outlines key categories, their examples, and their roles in current treatment regimens

S/N	Category	Examples	Role
1	First-line drugs	Isoniazid, Rifampicin	Limited use in DR-TB
2	Fluoroquinolones	Levofloxacin, Moxifloxacin	Core drugs
3	Injectables	Amikacin, Kanamycin	Intensive phase (less used now)
4	Oral second-line	Ethionamide, Cycloserine, PAS	Supportive drugs
5	New drugs	Bedaquiline, Delamanid, Pretomanid	Key role in modern regimens

14 Adverse drug reactions and management

The treatment of drug-resistant tuberculosis (DR-TB) involves prolonged use of multiple second-line and newer drugs, which are often associated with significant adverse drug reactions (ADRs). These toxicities can affect treatment adherence and outcomes, making early recognition and proper management essential.

14.1 Common toxicities

Adverse effects vary depending on the drugs used, but some commonly observed toxicities include:

- Gastrointestinal disturbances - nausea, vomiting, abdominal discomfort
- Hepatotoxicity - associated with drugs like pyrazinamide and ethionamide
- Neurotoxicity - peripheral neuropathy (e.g., linezolid, cycloserine)

- Ototoxicity - hearing loss due to injectable agents such as amikacin
- Nephrotoxicity - kidney damage caused by aminoglycosides
- Cardiotoxicity - QT interval prolongation (e.g., bedaquiline, delamanid)
- Psychiatric symptoms - depression, psychosis (e.g., cycloserine)

14.2 Monitoring strategies

Regular monitoring is essential to detect adverse effects early and prevent complications. Key strategies include:

- Baseline evaluation before starting treatment (liver function, renal function, ECG)
- Periodic laboratory tests during treatment (LFT, RFT, electrolytes)
- Audiometry for patients receiving injectable drugs
- ECG monitoring for patients on QT-prolonging drugs

- Clinical assessment for neurological and psychiatric symptoms

14.3 Management Approaches

Effective management of ADRs helps ensure treatment continuation and better outcomes:

- Dose adjustment or temporary discontinuation of the offending drug
- Substitution with alternative drugs when necessary
- Symptomatic treatment (e.g., antiemetics for nausea,

vitamin B6 for neuropathy)

- Close follow-up and counselling to improve adherence
- Multidisciplinary care, including specialist consultation in severe cases

To highlight common toxicities and their management during therapy, Table 08: Adverse Effects and Management provide a brief overview of associated drugs and recommended interventions.

Table 8: Adverse Effects and Management provide a brief overview of associated drugs and recommended interventions

S/N	Toxicity	Common Drugs	Management
1	Hepatotoxicity	Pyrazinamide, Ethionamide	Monitor LFT, stop/reduce drug
2	Neurotoxicity	Linezolid, Cycloserine	Vitamin B6, dose adjustment
3	Ototoxicity	Amikacin, Kanamycin	Audiometry, discontinue drug
4	Nephrotoxicity	Aminoglycosides	Monitor renal function
5	Cardiotoxicity	Bedaquiline, Delamanid	ECG monitoring
6	GI disturbances	Multiple drugs	Symptomatic treatment

15. Treatment adherence and patient support

Successful management of drug-resistant tuberculosis (DR-TB) depends not only on effective drug regimens but also on strong treatment adherence and comprehensive patient support. Given the long duration, high pill burden, and potential adverse effects of therapy, ensuring adherence is essential to achieve cure and prevent further drug resistance.

15.1 DOTS strategy (Directly Observed Treatment, Short-Course)

The DOTS strategy is a key component of TB control programs and aims to ensure that patients take their medications correctly under supervision. In DR-TB management, modified forms of DOT are used, where healthcare providers or trained supporters observe drug intake. This approach helps reduce treatment default, improves adherence, and enhances treatment success rates.

15.2 Psychological and Social support

Patients undergoing DR-TB treatment often face psychological stress, stigma, and social isolation. Long treatment duration and side effects can further affect mental health. Providing counselling, mental health support, and family involvement is essential to maintain motivation and adherence. Social support measures such as financial assistance, community-based care, and reducing stigma also play a crucial role in improving treatment outcomes.

15.3 Nutritional support

Malnutrition is common among TB patients and can weaken immunity and delay recovery. Adequate nutritional support is important to improve treatment response and overall health. Patients should receive a balanced diet rich in proteins, vitamins, and minerals. In many programs, nutritional supplementation is provided to support recovery and enhance treatment adherence.

16. Surgical management of drug-resistant tuberculosis

Although pharmacological therapy remains the cornerstone of treatment, surgical intervention can play an important adjunctive role in selected patients with drug-resistant tuberculosis (DR-TB), particularly when medical therapy alone is insufficient.

16.1 Indications

Surgical management is considered in carefully selected cases, including:

- Localized disease that is confined to a specific lung segment or lobe
- Persistent sputum positivity despite adequate and prolonged chemotherapy
- Extensive drug resistance (e.g., XDR-TB) with limited effective drug options
- Complications such as massive hemoptysis, destroyed lung, or bronchiectasis
- Failure of medical treatment or relapse after therapy

Procedures commonly include lobectomy, segmentectomy, or pneumonectomy, depending on the extent of disease.\

16.2 Outcomes

When performed in appropriate patients and combined with effective anti-TB therapy, surgical intervention can improve treatment outcomes. It helps reduce bacterial load, improves chances of culture conversion, and decreases the risk of relapse. Studies have shown higher treatment success rates in selected patients undergoing surgery compared to medical therapy alone.

However, surgery carries risks such as postoperative complications, respiratory impairment, and the need for specialized surgical expertise. Therefore, careful patient selection, preoperative assessment, and postoperative care are essential for achieving favourable outcomes.

17 Challenges in clinical management of drug-resistant tuberculosis

The clinical management of drug-resistant tuberculosis (DR-TB) remains highly challenging despite recent advances in diagnostics and treatment. Multiple factors affect treatment success and contribute to ongoing transmission.

17.1 Drug toxicity

Second-line and newer anti-tubercular drugs are often associated with significant adverse effects. These include hepatotoxicity, neurotoxicity, ototoxicity, and cardiotoxicity. Such toxicities can lead to dose modification, treatment interruption, or discontinuation, ultimately affecting treatment outcomes.

17.2 Long duration of treatment

Treatment of DR-TB typically requires prolonged therapy, ranging from 9 months to over 18-24 months. The long duration increases the risk of poor adherence, treatment fatigue, and loss to follow-up, which may result in treatment failure or relapse.

17.3 Cost burden

The management of DR-TB is expensive due to the high cost of second-line drugs, diagnostic tests, and long-term monitoring. This financial burden can be particularly challenging in low- and middle-income countries, where access to healthcare resources is limited.

17.4 Diagnostic gaps

Early and accurate diagnosis of DR-TB remains a major challenge. Limited access to advanced diagnostic tools, delays in detecting resistance, and inadequate laboratory infrastructure contribute to underdiagnosis and inappropriate treatment. These gaps allow continued transmission of resistant strains in the community (Ormerod, 2005; Seung *et al.*, 2015; Tan *et al.*, 2025; Vishwakarma *et al.*, 2023) ^[16].

18 Recent advances and future directions in drug-resistant tuberculosis

Significant progress has been made in recent years in the management of drug-resistant tuberculosis (DR-TB). Advances in drug development, treatment strategies, and research approaches are improving outcomes and offering new hope for better disease control.

18.1 New drug regimens (BPaL and All-Oral Regimens)

The introduction of newer drugs has led to the development of effective all-oral treatment regimens, reducing the need for injectable agents. The BPaL regimen (bedaquiline, pretomanid, and linezolid) has shown promising results, especially in MDR-TB and XDR-TB patients. Modified regimens such as BPaLM (with moxifloxacin) further enhance treatment effectiveness and reduce toxicity.

18.2 Shorter treatment regimens

Efforts are ongoing to shorten the duration of DR-TB treatment. New regimens lasting 6 to 9 months have been introduced, compared to traditional treatments lasting 18-24 months. Shorter regimens improve patient adherence, reduce side effects, and lower treatment costs.

18.3 Vaccine research

Vaccine development remains a key area of research in TB control. While the BCG vaccine provides limited protection, several new vaccine candidates are currently under clinical trials. These aim to improve protection against pulmonary TB and prevent progression from latent to active disease.

18.4 Personalized medicine

Advances in molecular diagnostics and genomics are enabling more individualized treatment approaches. Drug susceptibility testing and genetic profiling of *Mycobacterium tuberculosis* allow tailored treatment regimens based on resistance patterns. Personalized medicine has the potential to improve treatment success rates and minimize adverse effects.

19 Conclusion

Drug-resistant tuberculosis remains a major global health challenge, significantly complicating the control and

management of TB. The emergence of multidrug-resistant and extensively drug-resistant forms has reduced the effectiveness of standard treatment and increased the burden on healthcare systems. The development of resistance is closely linked to spontaneous genetic mutations, which are further amplified by improper treatment practices, poor adherence, and gaps in healthcare delivery.

Although significant progress has been made in recent years, including the introduction of rapid diagnostic tools and newer drugs such as bedaquiline, delamanid, and pretomanid, several challenges still persist. Long treatment duration, drug toxicity, high costs, and limited access to diagnostic and treatment facilities continue to affect patient outcomes.

Effective management of drug-resistant TB requires a comprehensive and patient-centred approach. Early diagnosis, appropriate drug selection, adherence support, and regular monitoring are essential components of successful treatment. In addition, strengthening public health systems, improving access to care, and ensuring rational use of anti-tubercular drugs are critical to prevent further emergence of resistance.

Future efforts should focus on the development of shorter and safer treatment regimens, advancement in vaccine research, and the implementation of personalized treatment strategies. A coordinated global effort is necessary to reduce the burden of drug-resistant tuberculosis and move towards the goal of TB elimination.

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