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Review Article

Drug-Resistant Tuberculosis at the Crossroads: Molecular Insights and Next-Generation Therapeutics

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ABSTRACT

Tuberculosis (TB) growing prevalence of drug-resistant strains *Mycobacterium tuberculosis*, it continues to major worldwide disease and a major public health concern. Emergence of Extensively Drug-Resistant (XDR-TB), Multidrug-Resistant (MDR-TB) tuberculosis has confounded disease management globally and dramatically decreased the efficacy of traditional anti-tubercular therapy. Drug resistance mainly occurs through genetic mutations, improper drug usage, poor patient compliance, prolonged treatment duration, and activation of resistance mechanisms such as efflux pumps. They play an important role reducing intracellular drug concentration, thereby decreasing therapeutic efficacy and promoting multidrug resistance. This review summarizes the pathogenesis of tuberculosis, mechanisms of anti-tubercular drug resistance, and the contribution efflux pumps resistant TB strains. It also highlights current diagnostic approaches, including molecular and phenotypic techniques used for early detection of resistant tuberculosis. In addition, emerging therapeutic strategies such as efflux pump inhibitors, novel anti-tubercular agents, combination therapy, are discussed as promising approaches for overcoming drug resistance. Despite recent advances, challenges including prolonged treatment duration, adverse drug reactions, treatment failure, and limited diagnostic accessibility continue to affect TB control programs. This emphasizes the importance of early diagnosis, effective therapeutic strategies, and continued research to combat drug-resistant tuberculosis and reduce its global burden.

Keywords: Anti-tubercular Drugs, Drug Resistance, Efflux Pumps, Multidrug-resistant Tuberculosis, *Mycobacterium tuberculosis*, Tuberculosis Diagnosis, Tuberculosis.

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INTRODUCTION

In 2020, TB killed almost 1.5 million people, making it global health concern (World Health Organization, 2021). The peculiar ability pathogenic bacterium, M. TB, thrive inside human body makes tuberculosis treatment difficult. The bacteria that cause TB are airborne pathogens. Although, TB affects brain, kidneys, spine, lungs, and other organs. TB typically curable (Vishwakarma *et al*., 2023). Because bacteria spread quickly in the environment, communicable diseases have always been a significant worldwide health issue. In densely crowded places, it seems more difficult to control the spread of disease from person to person. TB one of the top 10 causes of death worldwide leading cause of mortality by infectious diseases. According WHO 2019 tuberculosis report, 1.2 million HIV-negative people and 2,51,000 HIV-positive people died from TB in 2018 (Sileshi *et al*., 2021a). The primary causes of the increasing incidence spinal tuberculosis affluent nations are rise immunocompromised populations, particularly those with HIV, development drug-resistant strains (Singh *et al*., 2025). First-line drugs (isoniazid, pyrazinamide, rifampicin, and ethambutol) are administered long-term drug combinations with more toxic, costly, and ineffective second-line drugs (fluoroquinolones, aminoglycosides, and clofazimine) (Abdelrahman *et al*., 2022). Furthermore, it is frequently reported that bacterial tuberculosis strains become resistant to many medications during the course of treatment, which results in therapeutic failure (Sarkar *et al*., 2022). Attempting to increase medicine bioavailability and reduce side effects, Through the development of medication delivery systems based on nanoparticles, nanotechnology created platform to address challenges treatment and management of diseases (Tella *et al*., 2022). For more than 40 years, a lot of work has been done to find anti-TB medications, however the newly created compounds are thought to be cytotoxic and have low efficacy due to the advent of resistant bacterial strains. The unique cell-wall structure of Mycobacterium TB, consisting of mycolic acid, arabinogalactan, and covalently bound Peptidoglycan (PG), contributes to both

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the pathogens success and its natural resistance to numerous antimicrobial medications (Maitra *et al.*, 2021).

METHODOLOGY

Using electronic to create the current review study, a comprehensive literature search carried out using scientific databases like PubMed, Scopus, Google Scholar, Web of Science, and ScienceDirect. Using terms such anti-tubercular medications, efflux pumps, drug resistance mechanisms, nanotechnology in TB, MDR-TB, XDR-TB, and novel drug delivery systems, pertinent literature about tuberculosis and anti-tubercular drug resistance. This review covered peer-reviewed research publications. clinical studies, and recent scientific reports that were primarily published between 2020 and 2025. We examined and compiled articles that addressed the pathophysiology of tuberculosis, causes of resistance, diagnostic techniques, and new therapy methods. To thorough coverage of the subject, additional references were found in the bibliographies of certain articles.

Mycobacterium tuberculosis

Drug-metabolizing enzymes M. TB develop resistance multiple types antibiotics. Additionally, the bacilli include efflux mechanisms that can reduce target interaction and intracellular accumulation (Bhagwat *et al.*, 2022a). Roughly one-third of people worldwide have an asymptomatic MTB infection. Which kills over 50,000 people per week (Pawar *et al.*, 2020). The F0 protein *in vitro* sample isolates is encoded by the M. TB gene. Adenosine Triphosphate (ATP) is produced during The F0 protein drives rotation γ subunit between α3 β3 hexamers of F1, which is connected to the cylindrical ring of the c subunit, which produces ATP (Setyawan *et al.*, 2023).

Unique cell wall composition

Drug-degrading enzymes and thick, waxy, densely packed cell walls are the causes of this innate resistance. All the bacteria, Mycobacterium TB (Mtb) has arguably the most intricate cell wall. The plasma membrane is linked to Peptidoglycan (PG), Lipopolysaccharide (LM), and Lipopolysaccharide (LAM). which reach the outside membrane through the periplasm (Diab *et al.*, 2025a). Compared to other bacteria, the M. TB cell wall significantly less permeable chemotherapy medications. Hydrophilic molecules flow more readily through channels loaded with water, but small hydrophobic molecules pass swiftly through mycobacterial cell wall. Cell wall of mycobacteria distinct macromolecular structure is somewhat comparable to both Gram-positive and Gram-negative bacteria. It contributes to both pathogenicity and structural integrity and is essential for cell survival (Abrahams and Besra, 2021).

Slow growth and intracellular survival

Mycobacteria unusual cellular growth and division are one way they produce cell-to-cell deterministic heterogeneity. Mycobacteria lack the ruler that permits the division site to be accommodated at the cells center, other rod-shaped bacilli elongate in spiral pattern bacterium main body and divide by producing similar cells (Boldrin *et al.*, 2020). In addition to these components, several lipid components are accessible, such as Glycophospholipids and non-covalently bonded waxes are essential to the pathophysiology and survival of MTB because they act as a permeability barrier to drugs (Belete *et al.*, 2022a).

Role in drug resistance

The aminoglycosides and fluroquinolones, as well as first-line medications such pyrazinamide, ethambutol, rifampicin, and isoniazid, similar to XDR TB and fully drug-resistant TB strains, respectively (Arrigoni *et al.*, 2022). Ethambutol and pyrazinamide are the next most effective first-line drugs treating M. TB, after isoniazid and Rifampicin (RMP). Second-line treatments, which might take up to 20 months to finish, are used when these drugs fail to treat a patient. In 2022, Daniel and Bhakta Based drug resistance the infecting strain, TB is divided into three main categories: DS-TB, MDR-TB, XDR-TB. The most prevalent type of tuberculosis worldwide is DS-TB (Teneva *et al.*, 2023).

Classification of Anti-Tubercular Drugs

First-line anti-tubercular drugs

The Early clinical trials first-line anti-TB drugs like Pyrazinamide (PZA), Isoniazid (INH), Ethambutol (EMB), RMP showed a 95% cure rate; however, success rates can drop low, 65% in some areas (Table 1) (Sileshi *et al.*, 2021b). Adverse effects to first-line anti-TB medications are mostly the cause of their discontinuation. There may be a chance of morbidity and death during TB treatment, especially if drug-induced hepatitis occurs (Imam *et al.*, 2020). Stops RNA synthesis and cell death by inhibiting the DNA-dependent RNA polymerase of mycobacteria. Clofazimine and first-line TB medications, especially rifampicin, worked in concert to reduce and eradicate the growth of actively replicating bacteria (Staden *et al.*, 2023).

Second-line anti-tubercular drugs

The WHO, in essence second-line drugs, less effective and more dangerous compare the first-line drugs. Second-line anti-TB pharmaceuticals mostly used to treat multi-drug-resistant TB when first-line anti-TB medications cannot administer because resistance or intolerance. Second-line medications include aminoglycosides (kanamycin and amikacin), polypeptides (capreomycin, viomycin, and enviomycin), fluoroquinolones (ofloxacin, ciprofloxacin, and gatifloxacin), D-cycloserine, and thioamides. Second-line anti-tubercular drugs such fluoroquinolones, bedaquiline, linezolid, and clofazimine are essential when first-line therapy fails to treat multidrug-resistant tuberculosis (Lam *et al.*, 2020). Drug susceptibility testing is crucial for successful customized treatment, as evidenced by

molecular studies that show growing resistance to various drugs (Zheng *et al.*, 2021).

Types of Tuberculosis Based on Drug Resistance

Drug-sensitive tuberculosis

A case of tuberculosis that excretes Bacteria that are resistant DR-TB caused by resistance one or more anti-TB drugs (Table 2). Many types DR-TB include extensively XDR-TB, poly-DR-TB, Rifampicin-Resistant TB (RR-TB), and monodrug-resistant TB (mono-DR-TB) (A. Singh *et al.*, 2020). Early detection of drug resistance is critical to illness management. By gaining cumulative mutations that result in Multidrug Resistance (MDR), a single drug can become resistant to numerous treatments (Stephanie *et al.*, 2021).

Multidrug-Resistant TB (MDR-TB)

When patients have consistently failed MDR-TB is a prevalent cause of relapse and treatment resistance due to inconsistent treatment with usual short-course and relapse regimens. Standard first-line TB medications are nearly ineffective for those with MDR-TB (Lv *et al.*, 2024). Although TB can be cured, the therapy is difficult and necessitates daily medication for six months. These regimens were suggested by the WHO, which also divided them into short and long treatment regimens according on how long they lasted. A long regimen lasts 18-20 months (at least 15 months later culture conversion), although brief protocol is recommended to last 9-11 months (Nugraha *et al.*, 2021).

Totally drug-resistant TB (TDR-TB)

The strain M. TB that resistant to all first-line drugs (isoniazid, rifampicin, *Streptomyces*, pyrazinamide, and ethambutol) and second-line drugs (ethionamide, para-amino salicylic acid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin, and kanamycin) referred "totally drug resistant" failure of first- and second-line drugs, such as fluoroquinolones, compelled scientists develop more stronger drugs and novel drug delivery strategies combat drug resistance, even though TB chemotherapy is still employed (Suman *et al.*, 2023).

Extensively Drug-Resistant TB (XDR-TB)

Based on further DST for second-line anti-TB drugs, MDR-TB is classified as either XDR-TB or Pre XDR-TB. In the pre-Bedaquiline era, former is referred to as pre-XDR-TB (FQ) and latter pre-XDR-TB (SLI). MDR-TB with extra resistance to FQ and SLI is called XDR-TB (Utpat *et al.*, 2023). Recently, XDR-TB has become more common. Furthermore, it demonstrated that XDR-TB patients had far higher rates of poorer outcomes (death, treatment failure, or default) than non-XDR-TB patients. Given the extent issue, controlling XDR-TB vital worldwide health concern. Effectively address global health issue, more information about the risk factors adverse outcomes associated with this virus is needed (Varshney *et al.*, 2021).

MECHANISMS OF ANTI-TUBERCULAR DRUG RESISTANCE

Genetic mutations

Occasionally, a number of environmental circumstances result in genetic alterations or M. TB genomic alterations that both increase the probability that M. TB would survive in any extreme circumstance might lessen the therapy's efficacy (Table 3 and Figure 1) (Swain *et al.*, 2020a). One most widely used methods isolating resistant mutants and describing chromosomal alterations. It can provide valuable information about potential targets as well as insight cause or mechanisms of resistance. The primary objectives of these studies have been to ascertain the incidence of resistance and identify mutations that lead high level resistance (Bhagwat *et al.*, 2022b).

Target modification

The most common acyltrehalose in M. TB is Polyacyltrehalose (PAT), which, along with Diacyltrehalose (DAT), has a structural

Table 1: Anti-Tubercular Drugs and Their Mechanisms.

Drug Class	Drug Name(s)	Mechanism of Action	Reference(s)
First-Line	Isoniazid (INH)	Inhibits mycolic acid synthesis	(Singh *et al.*, 2025; Swain *et al.*, 2020a; Omoteso *et al.*, 2025).
	Rifampicin (RIF)	Inhibits RNA polymerase	(Singh *et al.*, 2025; Swain *et al.*, 2020a; Omoteso *et al.*, 2025; Varshney *et al.*, 2021).
	Pyrazinamide (PZA)	Converted to pyrazinoic acid; disrupts membrane	(Singh *et al.*, 2025; Swain *et al.*, 2020a).
	Ethambutol (EMB)	Inhibits arabinogalactan synthesis	(Singh *et al.*, 2025; Swain *et al.*, 2020a).
Second-Line	Fluoroquinolones	Inhibits DNA gyrase	(Rodrigues *et al.*, 2020; Chen *et al.*, 2025).
	Aminoglycosides (e.g., Amikacin)	Inhibits protein synthesis	(Rodrigues *et al.*, 2020).
	Bedaquiline	Inhibits ATP synthase	(Chen *et al.*, 2025).
	Linezolid	Inhibits 50S ribosomal subunit	(Chen *et al.*, 2025).

Table 2: Diagnostic Approaches for Drug-Resistant TB.

Diagnostic Method	Type	Key Features	Reference(s)
Phenotypic Drug Susceptibility Testing	Culture-based	Measures growth in presence of drugs	(Gajic *et al.*, 2022; Zack *et al.*, 2024).
Nucleic Acid Amplification Techniques (NATs)	Molecular	Rapid pathogen identification	(Omoteso *et al.*, 2025; Rai and Mehra, 2021).
High-Resolution CT	Imaging	Detects miliary lesions and organ damage	(Larkins-Ford and Aldridge, 2023 Staden *et al.*, 2023).
Chest X-ray	Imaging	Shows pulmonary TB patterns	(Larkins-Ford and Aldridge, 2023 Staden *et al.*, 2023).
Acid-Fast Stain (AFB)	Microscopy	Low sensitivity but widely used	Sreekantan *et al.*, 2022

role in the cell envelope and, by encouraging intracellular survival and affecting host immunological responses, helps M. TB replicate and stay in the host. The antibiotics in the diarylquinoline and imidazopyridine amide families target M. TB ATP production, the fluoroquinolone class inhibits M. TB DNA gyrase, and PAS inhibits DNA precursor (Swain *et al.*, 2020b).

Reduced cell wall permeability

It offers intrinsic resistance; the cell wall of Microorganisms depends on M. TB to survive. Drug-degrading enzymes and thick, waxy, densely packed cell walls are the causes of this innate resistance. Since synthetic enzymes lack human homologs, cell wall production provides a number of new targets (Belete, 2022b). Phospholipids based on glycerol, mainly phosphatidylethanolamines, make up the first plasma membrane of M.TB The plasma membrane is connected to PG, LM, and LAM, which extend across the periplasm into the outer membrane (Diab *et al.*, 2025b). Mycobacterial glycolipids interact with host cell receptors to facilitate bacterial proliferation by promoting internalization of bacilli and altering the immunological response. The substantial decrease in rifampicin permeability that capsular outer layer imposed M. TB cells rifampicin-surviving population can explained by a variety of factors, some of which may be related to the biophysical properties and/or composition of the capsular outer layer (Sebastian *et al.*, 2020).

Efflux pump overexpression

Efflux is a physiological process that keeps cells functioning normally by eliminating external materials and endogenous metabolic waste using an efflux pump. Bacterial resistance many antibiotic classes primarily caused by increased expression multi-drug efflux mechanisms. Efflux can carry a range of substrates or some antibiotics out of cells (Kumar *et al.*, 2025). Many different species, including eukaryotes both Gram-positive and Gram-negative bacteria, have membrane proteins known as efflux pump systems. ABC, PACE, MATE, SMR, and Major Facilitator Superfamily (MFS). These transporters are grouped into several families based structural characteristics and energy needs, including Resistance Nodulation Division (RND) superfamily (Rodrigues *et al.*, 2020).

DRUG-SPECIFIC RESISTANCE MECHANISMS

Isoniazid resistance

The Intracellular conversion of the prodrug Isoniazid (INH) Catalase-peroxidase KatG converts isonicotinoyl to isonicotinoyl-NAD, which then binds to NAD+. Ionicotinoyl-NAD negatively affects cell wall integrity blocking InhA, an enzyme necessary for synthesis of mycolic acid, a lipid found in bacterial cell walls (Goossens *et al.*, 2020). A number recent studies shown individuals with Hr-TB had worse outcomes than with drug-susceptible TB when treated with first-line medicines alone, even if INH not associated poor outcomes. Thus, it is crucial to recognize and treat Hr-TB as soon as possible (Kwak *et al.*, 2020). A synthetic antibacterial medication called INH has a bactericidal action on M. TB. By interfering with the manufacture of mycobacteric acid and causing cell wall rupture, INA has a high selectivity to stop the growth of MTB, while it has little effect on other bacteria. Additionally, it has been demonstrated that INA can be used in conjunction with other antibiotics, such as amikacin, cefotaxime, or imipenem, to treat MTB and lessen the development of resistance (Chen *et al.*, 2025).

Rifampicin resistance

RIF interacts with RNA polymerase's β-subunit to stop DNA-directed RNA production. The most common source of RIF resistance in M. TB isolates mutations rpoB gene. 95% strains have this mutation in the 81-base pair RRDR. Up to 90% RIF-resistant bacteria have mutations in codons 516, 526, and 531 within this 81-bp area (Malenfant *et al.*, 2021). Treating and controlling drug-resistant tuberculosis has proved difficult. RIF, a medication that has been used to treat TB for over fifty years, is still a crucial first-line treatment. The most popular RIF for treating tuberculosis is still RIF. Research areas are increasingly paying more attention to the resistance mechanisms of RIF (Xu *et al.*, 2021).

Pyrazinamide resistance

In terms of mode of action, we know that in the cytoplasm of M. TB, pyrazinamidase/nicotinamidase (PZase) hydrolyzes the prodrug PZA to Pyrazinoic Acid (POA). This amidase, which is part of the salvage mechanism for the synthesis of the vital coenzyme NAD and is encoded by pncA. PZA resistance in clinical isolates is most frequently caused by pncA. identified throughout the 561-bp open reading frame (Lamont *et al.*, 2020). Resistance to PZA with mutations pncA gene and its promoter; more recent research found the rpsA and panD genes. However, not all mutations in genes result in phenotypic resistance. Due to the lack quick and accurate phenotypic DST method, PZA is typically included to MDR-TB therapy regimens without its susceptibility testing (Naluyange *et al.*, 2020).

ROLE OF EFFLUX PUMPS IN TUBERCULOSIS RESISTANCE

Types of efflux pumps

Both host-induced and drug-induced tolerance have been shown to depend on efflux pumps. Drug tolerance and macrophage-induced efflux pumps have been connected in M. TB living in macrophages. It has been hypothesized that low-level efflux pump expression promotes evolution toward greater resistance (Rai and Mehra, 2021). The majority of transporters in the main facilitator superfamily carry 12 or 14 membrane segments, and their architectures typically contain 10 to 14 transmembrane α-helices. Furthermore, there are two common kinds of global bundles in the structures. Two fundamentally symmetrical bundles make up the first type of bundle, which is structural in nature (Kumar *et al.*, 2020).

Contribution to multidrug resistance

MDR-TB is frequently found Relapse and treatment resistance may result in patients who have repeatedly had irregular treatment failures with conventional short-course and relapse regimens. Numerous multidrug efflux pumps are found in bacteria, according to postgenomic research (Nishino *et al.*, 2021). MDR, the process by which tumours develop resistance to chemotherapy medications, is an important factor in chemotherapy therapies failure. MDR, the process through which cancers become resistant to drugs used in chemotherapy, is significant factor in failure of many chemotherapy regimens. Cancer is treated with several types of chemotherapy medicines, either by themselves or in conjunction with other agents. The chemical makeup of these substances varies (Mahinfar *et al.*, 2022).

Efflux pump inhibitors

Drug transport may be rendered inactive by Efflux Pump Inhibitors, (EPIs) which use one or more methods to stop efflux pumps. EPIs can be added to antibiotics as adjuvants to boost their effectiveness against bacteria that develop efflux pumps and to boost the effectiveness of drugs that are no longer effective against a pathogen (Zhang *et al.*, 2023). One possible way to fight antibiotic resistance is with (EPIs). By inhibiting their efflux pumps, EPIs aim to resistant bacteria vulnerable to the intended antibiotic. They can accomplish this by a number render of methods, such as competitive or non-competitive inhibition and the reduction proton gradient needed by efflux pumps to export antibiotics and other substrates (Zack *et al.*, 2024).

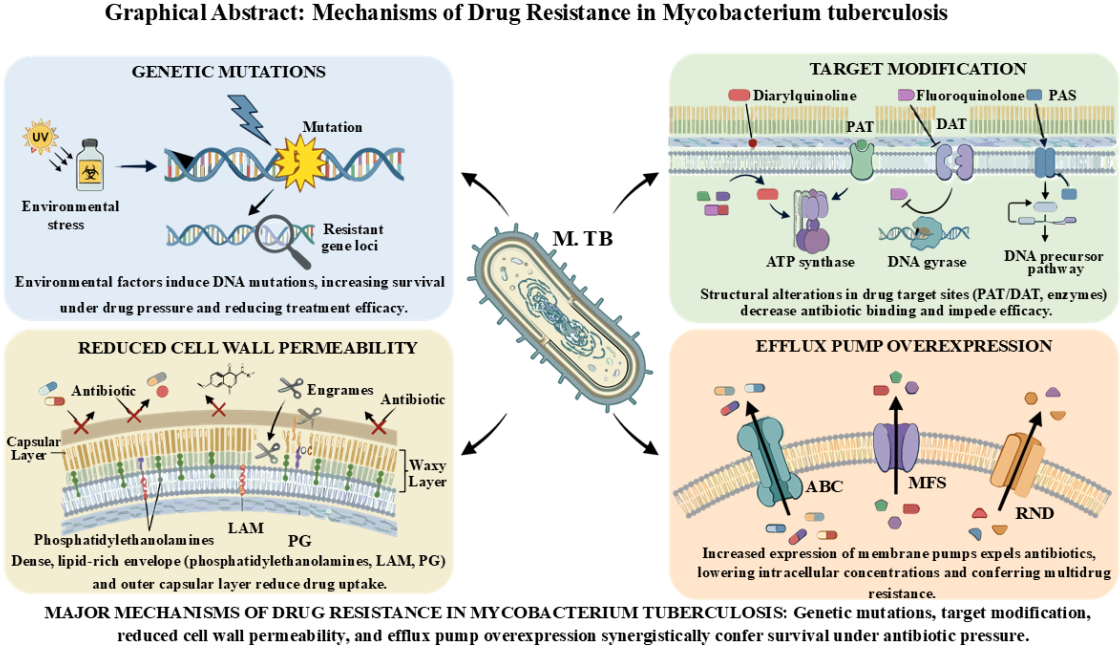

Figure 1: Mechanisms of Drug Resistance in *Mycobacterium tuberculosis*.

Table 3: Mechanisms of Anti-Tubercular Drug Resistance.

Mechanism	Description	Impact on Treatment	Reference(s)
Genetic Mutations	Mutations in target genes reduce drug binding (e.g., katG, rpoB, pncA)	Major cause of MDR and XDR resistance	(Imam *et al.*, 2020; Sebastian *et al.*, 2020; Sreekantan *et al.*, 2022).
Efflux Pump Overexpression	Increased efflux removes antibiotics from cells	Reduces intracellular drug efficacy	(Stephanie *et al.*, 2021; Malenfant *et al.*, 2021; Kumar *et al.*, 2025; Larkins-Ford and Aldridge, 2023).
Reduced Cell Wall Permeability	Thick, waxy cell wall limits drug entry	Intrinsic barrier to drug action	(Larkins-Ford and Aldridge, 2023 Staden *et al.*, 2023; Boldrin *et al.*, 2020; Diab *et al.*, 2025a; Mahinfar *et al.*, 2022).
Target Modification	Alteration in drug targets	Reduced susceptiblity to first-line drugs	Sreekantan *et al.* 2022
Non-Heritable Tolerance	Stress-induced survival strategies	Contributes to persister phenotypes	Omoteso *et al.* 2025

Table 4: Types of Drug-Resistant Tuberculosis.

Resistance Type	Definition	Treatment Challenges	Reference(s)
Drug-Susceptible TB (DS-TB)	Sensitive to first-line drugs	Standard short-course therapy	(Rai and Mehra, 20210; Diab *et al.*, 2025b; Varshney *et al.*, 2021; Bhagwat *et al.*, 2022a).
Mono/Poly-Resistant TB	Resistant to one or multiple drugs	Requires tailored regimens	(Rai and Mehra, 20210; Diab *et al.*, 2025b; Varshney *et al.*, 2021; Bhagwat *et al.*, 2022a).
Rifampicin-Resistant TB (RR-TB)	Resistant to RIF with/without other drugs	Limited first-line options	(Rai and Mehra, 20210; Diab *et al.*, 2025b; Varshney *et al.*, 2021; Bhagwat *et al.*, 2022a).
Multidrug-Resistant TB (MDR-TB)	Resistant to INH and RIF	Difficult longer therapy	(Varshney *et al.*, 2021; Suman *et al.*, 2023; Stephanie *et al.*, 2021).
Extensively Drug-Resistant TB (XDR-TB)	MDR + resistance to FQs/ second-line injectables	Very poor prognosis	Imam *et al.*, 2020; Nugraha *et al.*, 2021; Utpat *et al.*, 2023; Abrahams and Besra, 2021).
Totally Drug-Resistant TB (TDR-TB)	Resistant to all first and second-line drugs	Extremely challenging	(Sileshi *et al.*, 2021b; Imam *et al.*, 2020).

DIAGNOSTIC APPROACHES FOR DRUG-RESISTANT TUBERCULOSIS

Phenotypic drug susceptibility testing

WHO advises universal DST (at least RIF resistance testing) and quick diagnoses for all individuals exhibiting clinical signs of active tuberculosis; however, this objective is unachievable with the techniques now in use (Table 4). For the diagnosis of M. TB, several genotypic and phenotypic DST diagnostic techniques are available (Sreekantan *et al.*, 2022). Phenotypic techniques created for AMR detection include colorimetric assays. Their basis is the bacterial enzyme hydrolyzing test component, may be detected variations in color and pH of chromogenic materials. In summary, bacterial suspension, bacterial lysate suspension combined with detection solution comprising antibiotics and pH indicator dyes, such as phenol red, and incubated for no more than few hours (Gajic *et al.*, 2022).

Molecular diagnostic techniques

M.TB is diagnosed using a mix of molecular, microbiological, imaging, and laboratory techniques. Chest X-rays usually show miliary pattern, but high-resolution CT imaging specifically detects miliary nodules, ground-glass opacities, interlobular septal thickening. Depending organs affected, further diagnostic imaging methods including ultrasound, MRI, Positron Emission Tomography-CT (PET-CT), or echocardiography are recommended assess extent organ damage. Pancytopenia, lymphopenia, anaemia, and elevated levels of bilirubin, transaminase, ESR, and CRP are typically found in MiliTB blood profiles (Gopalaswamy *et al.*, 2021).

CURRENT STRATEGIES TO OVERCOME DRUG RESISTANCE

Combination drug therapy

Due to the potential for non-specific resistance mechanisms, combining medications that target diverse targets is insufficient to prevent cross-resistance. Recent experience with bedaquiline monotherapy has shown that non-specific mechanisms, like enhanced drug efflux, may be involved in the rapid emergence of low-level clinical resistance (Bhagwat *et al.*, 2022c). We can better understand Mtb infections difficult to treat and necessitate

long-term multidrug therapy to the disease pathophysiology of tuberculosis. Multiple cell types that change as the disease progresses and is treated are part of the coordinated immune response that makes up the pathophysiology of pulmonary tuberculosis. Given how dynamic and complicated the infectious environment is, M. TB needs to be able to withstand a range of stresses and have the physiological adaptability to change with its surroundings (Larkins-Ford and Aldridge, 2023).

CHALLENGES AND LIMITATIONS

Drug-resistant TB still presents major treatment challenges because of its toxicity, high cost, and difficulty in reaching adequate drug concentrations at infection site. Even with the advent novel anti-TB medications like bedaquiline and delamanid. Although there is potential in novel strategies like tailored nanocarrier systems and repurposing already-approved medications, there are still significant obstacles in the areas of scalability, safety, and accessibility. This review emphasizes how increasing MDR-TB treatment results requires overcoming delivery and resistance mechanisms (Omoteso *et al.*, 2025).

CONCULSION

Due to the growth and spread drug-resistant M. TB strains, TB remains major global health concern. Both acquired and inherent resistance are impacted by the bacterium distinct cell wall and adaptive survival strategies. First and second-line anti-TB drugs are limited toxicity, long treatment durations, and increasing resistance, despite their continued importance. Effective treatment and prompt identification of resistant TB are made more difficult by diagnostic difficulties. Resistance is primarily caused by genetic mutations, overexpression of the efflux pump, and decreased drug permeability. Although the diagnosis of resistant strains has increased due to advancements in molecular diagnostics, wider deployment is still required. New approaches like efflux pump inhibitors and drug delivery via nanoparticles have the potential improve medication effectiveness and lessen adverse effects. Treatment results may be enhanced by combination therapy customized to resistance profiles. It is essential to conduct more study on the molecular causes of resistance and develop novel treatment strategies. Controlling and eventually lowering the burden of drug-resistant tuberculosis will require stepping up international public health initiatives and creating focused interventions.

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ABBREVIATIONS

ABC: ATP-Binding Cassette (efflux pump family); **ADLI:** Anti-Tuberculosis Drug-Induced Liver Injury; **AGP:** Arabinogalacto-Polysaccharide; **BCG:** Bacillus Calmette-Guérin; **CRP:** C-Reactive Protein; **CT:** Computed Tomography; **DST:** Drug Susceptibility Testing; **DS-TB:** Drug-Susceptible Tuberculosis; **EMB:** Ethambutol; **EPS:** Extracellular Polymeric Substances; **EPIs:** Efflux Pump Inhibitors; **FQ:** Fluoroquinolone; **HIV:** Human Immunodeficiency Virus; **INH:** Isoniazid; **LAM:** Lipoarabinomannan; **LM:** Lipomannan; **MDR:** Multidrug Resistance; **MDR-TB:** Multidrug-Resistant Tuberculosis; **MIC:** Minimum Inhibitory Concentration; **MTB:** Mycobacterium tuberculosis; **NATs:** Nucleic Acid Amplification Techniques; **PET-CT:** Positron Emission Tomography-Computed Tomography; **POA:** Pyrazinoic Acid; **PZA:** Pyrazinamide; **QNAT:** Quantitative Nucleic Acid Test; **RIF:** Rifampicin; **RR-TB:** Rifampicin-Resistant Tuberculosis; **ROS:** Reactive Oxygen Species; **SMR:** Small Multidrug Resistance (efflux pump family); **TB:** Tuberculosis; **TDM:** Trehalose Dimycolate; **TDR-TB:** Totally Drug-Resistant Tuberculosis; **WHO:** World Health Organization; **XDR-TB:** Extensively Drug-Resistant Tuberculosis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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