Journal of Young Pharmacists, 2024; 16(2):145-154.
https://www.jyoungpharm.org

Review Article

Current Challenges in the Management of Tuberculosis

Vivek Srivastava*, Ananya Verma

Department of Pharmacology, Amity institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh, INDIA.

ABSTRACT

The global fight against Tuberculosis (TB) persists; grappling with approximately 10.6 million new cases in 2021, as documented in the 2022 WHO Global TB Report.[1] Of concern is the escalating incidence of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB), which saw an estimated 450,000 new cases in the same year. Today's major problem in the treatment of *Mycobacterium* TB is drug resistance brought on by anti-TB therapy. The degree of resistance led to variations and other effects that eventually ended in death and health risks. The advent of certain drug-resistant strains of TB that are resistant to several treatments, prolonged drugs and all drugs is going to bring a major and catastrophic comeback to the disease. Current advancements in TB treatment help to reduce anti-tubercular medication resistance. Due to *Mycobacterium tuberculosis's* extraordinary flexibility, drug resistance in tuberculosis is a complicated phenomenon. Via genetic mutations, efflux pumps and other processes, these bacteria may become resistant to anti-TB medications. Hence, against drug-resistant bacteria, conventional TB treatment regimens-which usually include a mix of antibiotics-may stop working. The worldwide account will lose about 200,000 due to medication resistance fatalities in a single year. The development of vaccines against tuberculosis is a promising topic, but progress has been hampered by a lack of funding, organization and understanding of immunological responses. A Tubercular Vaccine Accelerator Council will combine resources and expertise to tackle these issues and accelerate development. Accomplish the WHO's goal of TB eradication by 2030.

Keywords: Challenges, Drugs, Mutation, Resistance, Tuberculosis.

Correspondence:
Dr. Vivek Srivastava
Department of Pharmacology, Amity institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh, INDIA.
Email: srivastavav696@gmail.com

Received: 05-02-2024;
Revised: 30-03-2024;
Accepted: 01-04-2024.

INTRODUCTION

Tuberculosis (TB) is a chronic inflammatory illness that is most often caused by the bacteria *Mycobacterium tuberculosis*. Mostly found in humans. Occasionally, the closely related mycobacteria *M. bovis, M. africanum* and *M. microtia* may cause similar diseases. *M. avium* complex (MAC), environmental Mycobacteria and a few less prevalent *Mycobacteria* comprise the *Mycobacterium tuberculosis* complex.[2] An extremely powerful bacteria that mostly causes typical pulmonary tuberculosis illness by attacking the lungs. In addition, extrapulmonary Tuberculosis (TB) may affect the brain, kidneys, spine, lymph nodes and all other organs and tissues.[3]

An overview on TB

Approximately 10 million individuals suffer from active tuberculosis each year, out of the two billion people, or one-fourth of the world's population, who carry TB germs. Globally, 1.6 million TB deaths occurred in 2021; 187,000 of those deaths were HIV-positive. The ongoing public health emergency and health security threat is multidrug-resistant tuberculosis. In 2021 studies saw therapy for about 1 in 3 patients with drug-resistant tuberculosis. 74 million fatalities between 2000 and 2021 are expected to be avoided by TB screening and treatment.[4] India's worst health problem now is tuberculosis. Based on reported cases, India leads the world in tuberculosis cases in 2019 with 2.4 million, the World Health Organisation announced. Just over 1.6 million cases of tuberculosis were recorded in India in 2020, suggesting that most illnesses were not reported following the COVID-19 pandemic, which halted TB surveillance and reporting.[2,4,6] High-burden tuberculosis is observed in HIV-positive people, healthcare personnel and recent immigrants from tuberculosis-endemic areas in more developed nations. There is also evidence of a higher risk when immunosuppressive medications, such as long-term corticosteroid therapy, are used. More recently, there has been evidence linking the use of a monoclonal antibody that targets Tumour Necrotic Factor alpha (TNF-alpha), an inflammatory cytokine, to an elevated risk.

Tuberculosis is transmitted through airborne droplets when an uninfected individual coughs, sneezes, talks, or spits, especially in crowded places. People with HIV/AIDS[5] or weakened immune systems are at a greater risk of contracting tuberculosis compared to healthy individuals. Tuberculosis can exist in both symptomatic and asymptomatic forms. Those with bacterial infections but no

DOI: 10.5530/jyp.2024.16.21

symptoms may develop latent or inactive tuberculosis.[7] Despite appearing dormant, tuberculosis remains within the body.

Tuberculosis is categorized into primary infection, where the body is initially invaded by the bacteria, sometimes presenting with symptoms such as fever or pulmonary symptoms or remaining asymptomatic. Active tuberculosis is a chronic disease, characterized by the continuous growth and spread of tuberculosis germs, potentially infecting others. Prompt treatment is crucial for minimizing complications and containing the spread of infection. Latent tuberculosis involves bacteria that are dormant and prevented from spreading by the immune system but can remerge at any time. Tuberculosis is a transmissible illness and immediate treatment is vital for containment. The World Health Organization classifies tuberculosis drug resistance into several types, including mono-resistance, poly-resistance, Multi-Drug Resistance (MDR), Extensive Drug Resistance (XDR) and Rifampicin Resistance (RR), each requiring specific management approaches to combat.[7-10]

When individuals with tuberculosis exhale through coughing, sneezing, speaking, or singing, they release bacteria into the air, which can infect nearby individuals upon inhalation. The bacteria traverse the upper and lower airways, infecting epithelial and microfold cells in nasal or bronchial mucosal tissue.[10] Alveolar macrophages, specialized immune cells, interact with airborne pathogens in the alveoli, where infection may occur.[5] Latent tuberculosis typically arises from successful containment by the immune system, but active illness can still develop. Once inhaled, the bacteria initiate their life cycle in the lungs and airways.[11] Primary infection occurs upon the initial contact of the bacillus with the airway.[12,13] Mycobacterium's ability to compromise the immune system leads to symptoms, with infection being the primary cause of 90% of complications.

Diagnostic procedures for tuberculosis involve an initial assessment, including a medical history review and physical examination to identify relevant symptoms and potential exposure. Diagnostic tests encompass various methods:

Sputum Sampling: Patients with chest abnormalities should provide three sputum samples on different days for examination.

Mantoux Test (Tuberculin skin test): Detects delayed hypersensitivity to tuberculin, evaluating cell-mediated immunity with results recorded after 48 to 72 hr.

Interferon Release Assays: Assess cell-mediated immunity through T cell stimulation *in vitro,* utilizing unique proteins.

Radiographic Examinations: Chest radiography is used for patients with latent tuberculosis or pulmonary symptoms.

Microbiological Examinations: Acid-Fast Bacilli (AFB) staining is a quick and cost-effective method, recommended alongside fluorescence microscopy for higher sensitivity. Presence of AFB in respiratory specimens strongly suggests tuberculosis, when considered with clinical and radiographic data.

Individuals in close contact with someone with pulmonary tuberculosis face the highest risk of contracting the disease, including family members, friends and those working in specific settings like group homes or hospitals for TB patients. Transmission through surface contact is minimal unless there's direct interaction such as handshakes or sharing utensils. Immunocompromised individuals, particularly those with HIV or malnutrition, are at heightened risk due to compromised immune systems. Other vulnerable groups include homeless individuals, prisoners, substance abusers, those on immunosuppressive drugs, people with kidney or diabetes issues, smokers, organ transplant recipients and pregnant women, especially the elderly, young children and infants.[14,15]

Treatment for Tuberculosis (TB) involves tailored regimens, including Pharmacological and Non-Pharmacological approaches. Pharmacological treatment categorizes anti-tubercular medications into first-line, second line and Special drugs based on clinical use, with First-line drugs like rifampicin and isoniazid being the initial choice due to their efficacy and low toxicity. Second-line drugs, such as fluoroquinolones, are used when first-line drugs are ineffective or intolerable, while Special drugs, including newer discoveries, are reserved for complex cases like MDR or XDR tuberculosis.[15] Lifestyle adjustments are emphasized in non-pharmacological approaches to enhance patients' overall well-being, addressing factors like healthcare access, living conditions, socioeconomic status and diet quality. Proper nutrition plays a crucial role in boosting immunity and supporting the body's ability to combat infection during TB treatment. However, socioeconomic challenges like cramped living conditions and poverty can hinder treatment success, while lifestyle habits such as substance abuse or smoking can worsen symptoms and reduce the effectiveness of TB medications.[16] The Directly Observed Therapy Short Course (DOTS)[17] ensures treatment adherence through political commitment, microscopy services, prescription availability, surveillance techniques and direct therapy supervision. This approach, lasting 6 to 8 months, varies in duration based on patient history, with 99DOTS offering a cost-effective digital solution to enhance medication adherence, particularly in regions like Himachal Pradesh, India.[18]

CHALLENGES IN MANAGEMENT OF TB

Combatting TB remains a significant challenge for global healthcare systems due to diagnostic complexities and evolving clinical presentations.[19] Access to Point-of-Care (POC) tests is hindered by limitations in remote areas despite advancements like the lateral flow urine LAM assay.[20,21] Diagnostic devices encounter errors, cost barriers and suitability issues, complicating TB diagnosis, particularly in children or extrapulmonary cases. Multidrug-Resistant TB (MDR-TB) adds further complexity,

requiring multifaceted strategies and collaboration among stakeholders to address diagnostic challenges. Additionally, TB-related stigma contributes to societal discrimination against patients, hindering timely diagnosis and treatment adherence.[22,23] Overcoming these hurdles necessitates comprehensive approaches involving education, community engagement and policy interventions to improve treatment outcomes and lessen the global TB burden.[24-26]

Drug resistance poses significant challenges in TB treatment, primarily due to resistance developed against anti-tubercular drugs. Resistance mechanisms vary among different drugs, impacting treatment efficacy and health risks. First-line drugs like Isoniazid, Rifampicin, Ethambutol, pyrazinamide and streptomycin.[27-30]

Second-line drugs like Fluoroquinolones, Para-aminosalicylic acid, Cycloserine, Kanamycin, Amikacin, Capreomycin, Terizidone, Prothionamide, Ethionamide, Rifabutin, Rifapentine.[28-36] Some of the newer drugs also show resistance shown in Table 1.

Resource constraints pose significant challenges in addressing Tuberculosis (TB) on a global scale, particularly in areas with limited resources. These constraints hinder effective TB management across various fronts. Limited resources impact TB diagnosis, with scarce access to advanced diagnostic tools leading to delays in detection and increased transmission rates. Treatment initiation and adherence are also affected, as free treatment often lacks additional diagnostics, impacting patient care and outcomes. Investments in accessible diagnostics, affordable treatment options and strengthening healthcare infrastructure are crucial steps to mitigate the impact of resource constraints on TB management, particularly in resource-limited settings.

Recent advancement and strategies to overcome the resistance in management of TB

The rise in *Mycobacterium tuberculosis* infections, driven by increased resistance to traditional antimicrobial agents, necessitates the development of new treatments. Several innovative antimicrobial drugs are currently under investigation for tuberculosis treatment. However, challenges such as limited profitability and the need for significant investment hinder pharmaceutical companies' efforts to create novel medications. Overcoming barriers like conducting clinical trials, discovering novel molecules effective against *M. tuberculosis* and obtaining

Table 1: Resistance caused by anti-tubercular drugs with their cross-resistance and resistance Class.[56-58]

Drug	Resistance Mechanism	Cross-Resistance Drugs/Class	Resistance Stage
First Line Drugs			
Rifampicin	Mutations in the rpoB gene, which encodes the RNA polymerase β subunit. These mutations interfere with the binding of rifampicin to the RNA polymerase, reducing its effectiveness. Rifampicin binds to the β subunit of RNA polymerase, inhibiting RNA synthesis. However, mutations in rpoB alter the structure of RNA polymerase, reducing the affinity of rifampicin for its binding site. Consequently, bacterial RNA synthesis continues despite the presence of rifampicin, leading to drug resistance.	Rifabutin, Rifapentine	XDR, MDR
Isoniazid	The katG gene mutation is the primary cause of isoniazid (INH) resistance, impacting enzyme function. In contrast, mutations in the inhA gene represent a secondary cause, lowering INH affinity and resulting in resistance. Mutations in ahpC, kasA, ndh, iniABC, fadE, furA, Rv1592c and Rv1772 also contribute to INH resistance, albeit less frequently observed compared to katG and inhA mutations[2]. Changes in drug activation or metabolism, particularly impaired INH activation by the KatG enzyme due to katG mutations, diminish INH's ability to kill bacteria. Additionally, mutations in the inhA gene reduce its binding affinity, diminishing INH's efficacy against *Mycobacterium tuberculosis*.	Ethionamide, protionamide	XDR, MDR
Pyrazinamide	The resistance mechanisms primarily involve mutations in the pncA gene, which codes for pyrazinamidase, the enzyme required to activate pyrazinamide. These mutations may lead to reduced or loss of pyrazinamidase activity, rendering pyrazinamide ineffective against the tuberculosis-causing bacteria. Additionally, alterations in the efflux pump system and mutations in other genes like rpsA and panD have also been associated with pyrazinamide resistance.	Delamanid	XDR, MDR

Drug	Resistance Mechanism	Cross-Resistance Drugs/Class	Resistance Stage
Ethambutol	Primarily involves mutations in the embB gene, particularly codons 306, 406 and 497, which encode the arabinosyl transferase enzyme. These mutations lead to altered enzyme activity, hindering the incorporation of arabinogalactan into the mycobacterial cell wall. Resistance can also arise from efflux pump mechanisms, reducing drug concentration inside the bacterial cell.	Terizidone	XDR, MDR
Streptomycin	Primarily occurs due to mutations in the rpsL and rrs genes. Mutations in rpsL gene (coding for ribosomal protein S12) alter the binding site of streptomycin, reducing its affinity. Mutations in the rrs gene (coding for 16S rRNA) interfere with streptomycin binding to the ribosome.	Kanamycin, Amikacin, Capreomycin	XDR, MDR
Second Line Drugs			
Fluoroquinolones	Primarily occurs due to mutations in the genes gyrA and gyrB, which encode subunits of DNA gyrase and inthe gene rrs, which encodes the 16S rRNA. These mutations hinder the binding of fluoroquinolones to their target sites, reducing their effectiveness. Additionally, mutations in the genes, which regulates the expression of aminoglycoside-modifying enzymes, can confer resistance to fluoroquinolones by potentially altering the permeability of the cell wall.	-	XDR
Ethionamide	Mutations in the EthA gene can lead to resistance to ethionamide by reducing the activity of the EthA enzyme, which is responsible for activating the drug. Some strains develop resistance by increasing the expression of efflux pumps, which decrease the amount of the drug inside the cell. Changes in the target enzyme, InhA, due to mutations in the inhA gene, can also make ethionamide less effective. Additionally, resistance may arise through the activation of alternative metabolic pathways that bypass EthA, making the drug ineffective.	Isoniazid, Pretomanid	XDR, MDR
Cycloserine	Primarily occurs through mutations in genes involved in cell wall biosynthesis, altering the target site of cycloserine. Cycloserine inhibits D-alanine racemase and D-alanine ligase, enzymes involved in peptidoglycan synthesis, leading to cell wall disruption. Mutations can affect these enzymes, reducing cycloserine's binding affinity and rendering it ineffective against the bacteria. Additionally, mutations in other genes related to cycloserine transport and metabolism contribute to resistance.	-	XDR, MDR
Para-aminosalicylic acid	Altered Target Site: Resistance can occur due to mutations in the gene folC, encoding Dihydropteroate Synthase (DHPS). Decreased Drug Uptake: Mutations in permease genes (such as iniB and iniC) can reduce the uptake of PAS into bacterial cells, leading to resistance. Increased Efflux Pump Activity: Overexpression of efflux pumps, such as iniA and iniB, can pump out PAS from bacterial cells, reducing its intracellular concentration and efficacy.	-	XDR, MDR
Prothionamide	Efflux Pump Overexpression: Bacteria can develop resistance to prothionamide by overexpressing efflux pumps, which actively remove the drug from the bacterial cell, reducing its concentration inside the cell and rendering it ineffective. Mutation in Drug Target: Mutations in enzymes targeted by prothionamide, such as mycobacterial InhA, can alter the binding site, reducing the drug's effectiveness. Altered Drug Activation: Alterations in the enzyme responsible for activating prothionamide can reduce its conversion to its active form, thereby lowering its efficacy against bacteria.	-	XDR, MDR

Drug	Resistance Mechanism	Cross-Resistance Drugs/Class	Resistance Stage
Terizidone	Primarily involves mutations that alter the target enzymes involved in cell wall synthesis, specifically l-alanine racemase and d-alanine ligase. These mutations reduce the binding affinity of Terizidone to these enzymes, rendering the drug less effective against the bacteria.	Ethambutol	XDR, MDR
Rifabutin	Bacteria activate efflux pumps to expel rifabutin, decreasing its concentration inside cells and efficacy. Mutations in the rpoB gene alter rifabutin's target binding site, reducing its effectiveness. Some bacteria produce enzymes that chemically modify rifabutin, rendering it inactive against bacterial growth. Changes in cell wall structure or membrane proteins reduce rifabutin's ability to enter cells, limiting its antibacterial action.	Rifampicin, Rifapentine	XDR, MDR
Rifapentine	A rifamycin antibiotic used to treat tuberculosis, typically occurs through mutations in the rpoB gene, which codes for the beta subunit of RNA polymerase. These mutations prevent Rifapentine from effectively binding to RNA polymerase, reducing its bactericidal activity. Additionally, efflux pumps may contribute to resistance by expelling Rifapentine from bacterial cells, reducing its intracellular concentration.	Rifampicin, Rifabutin	XDR, MDR
Kanamycin	Enzymatic Modification: Bacteria produce enzymes that chemically alter kanamycin, making it inactive. Reduced Uptake: Some bacteria limit kanamycin uptake by changing membrane permeability or transport proteins, preventing its entry into cells. Efflux Pump Overexpression: Bacteria increase efflux pumps to remove kanamycin from cells, lowering its effectiveness. Target Modification: Mutations in bacterial ribosomal sites decrease kanamycin's ability to bind effectively, reducing protein synthesis inhibition. Ribosomal Protection: Certain bacteria produce protective proteins that bind to ribosomes, preventing kanamycin from interfering with protein synthesis.	Streptomycin, Amikacin, Capreomycin	XDR, MDR
Amikacin	Efflux Pumps: Bacteria resist amikacin by increasing efflux pumps, expelling the drug from the cell and diminishing its effectiveness. Enzymatic Modification: Bacteria produce enzymes like Aminoglycoside-Modifying Enzymes (AMEs) that alter amikacin chemically, inhibiting its binding to target sites and reducing efficacy. Target Modification: Bacteria change ribosomal target sites, decreasing amikacin's binding affinity and impairing protein synthesis. Decreased Permeability: Bacterial membrane changes reduce amikacin uptake, limiting access to intracellular targets and reducing effectiveness. Biofilm Formation: Bacterial biofilms offer protection, limiting amikacin's penetration and altering metabolic activity, leading to resistance.	Streptomycin, Kanamycin, Capreomycin	XDR, MDR
Capreomycin	Efflux Pump Activation: Bacteria activate efflux pumps to expel Capreomycin, reducing its effectiveness. Target Alteration: Changes in Capreomycin's target site within bacteria reduce its binding affinity, diminishing its bactericidal effects. Enzymatic Inactivation: Bacteria produce enzymes that modify Capreomycin, rendering it inactive against tuberculosis bacteria.	Streptomycin, Kanamycin, Amikacin	XDR, MDR

Drug	Resistance Mechanism	Cross-Resistance Drugs/Class	Resistance Stage
Special Drugs/Newer Drug Class			
Delamanid	Mutations in Mycobacterium tuberculosis Genes: Mutations in ddn, encoding F420-dependent Ddn oxidoreductase, can cause delamanid resistance. Efflux Pump Activation: Activated efflux pumps in Mycobacterium tuberculosis expel delamanid, contributing to resistance. Altered Drug Target: Changes in delamanid's bacterial target hinder its effectiveness against Mycobacterium tuberculosis growth.	Pyrazinamide	XDR, MDR
Pretomanid	Mutations in Target Genes: Certain gene mutations, like panD and fadD32, linked to mycolic acid biosynthesis, provide resistance. Efflux Pumps: Enhanced efflux pump activity expels Pretomanid, lowering its cellular levels. Biofilm Formation: Bacterial biofilms offer protection against Pretomanid, aiding survival and resistance development.	Isoniazid, Ethionamide	XDR, MDR
Bedaquiline	Efflux Pump Activation: Bacteria may develop resistance to Bedaquiline by activating efflux pumps, which expel the drug from the bacterial cell, reducing its effectiveness. This mechanism is part of the multifactorial resistance seen in tuberculosis treatment.	-	XDR, MDR

accurate laboratory specimens for therapy duration prediction is crucial. To enhance treatment effectiveness, both the discovery of new drugs and the modification of existing ones are essential approaches.[37-41]

Inhancing the Utilization of Current Medications

Traditional antibiotics historically effective against TB now encounter challenges such as drug resistance and prolonged treatment durations. To address this, adjustments are made to both old and new treatments to efficiently combat TB. Following rifamycin administration, optimal dosages of previous medications are determined. While increasing antitubercular drug dosages is often necessary for effective treatment, caution is required to avoid overdosing and potential toxicity. Healthcare providers strive to achieve therapeutic drug levels in the body to inhibit bacterial growth, overcome resistance and ensure treatment success. Tailoring dosages to individual variations in drug metabolism and absorption can enhance treatment consistency. However, vigilant monitoring is essential to detect any adverse effects. Therefore, careful observation and dose adjustments are critical for successful TB therapy, minimizing treatment failure and the emergence of drug-resistant strains.[42,43]

To develop effective treatments for TB

New antimicrobial agents must meet specific criteria. These include robust bactericidal properties to combat cross-resistance, optimal pharmacokinetic/pharmacodynamic qualities, compatibility with other medications, affordability, stability, narrow spectrum, high effectiveness and minimal risk of resistance emergence. The pursuit of these attributes aims to shorten treatment duration and enhance patient outcomes while reducing the incidence of drug-resistant TB. Current efforts involve researching and developing new antimicrobial drugs and therapies, as well as exploring innovative strategies to target and eliminate TB bacteria.[44-46] Understanding the mechanisms underlying drug tolerance and persistence in TB is crucial for developing novel therapeutic approaches.[47] A description of Newer Anti-microbial agents used in TB is shown in Table 2.

Repositioning of antitubercular drugs

Involves repurposing existing medications approved for other conditions to treat tuberculosis, leveraging their established safety and efficacy profiles to expedite the search for new TB therapies. Identifying drugs with proven antimycobacterial activity or the ability to target specific M. tuberculosis pathways is crucial for this strategy. By repurposing already-approved medications, researchers and healthcare providers can bypass costly and time-consuming drug development stages like initial clinical trials and safety testing. Certain medications, such as antiretrovirals like lopinavir/ritonavir, show promise in TB treatment due to their antimycobacterial properties. Screening initiatives have explored various drug classes, including statins, calcium channel blockers and NSAIDs, for potential anti-TB activity. Through high-throughput screening and computational methods, compounds targeting specific M. tuberculosis mechanisms have been identified, with some progressing to preclinical and clinical testing phases.[48-51]

In the realm of TB treatment, the emergence of Drug-Resistant (DR) strains poses challenges despite limited therapeutic options. Second and third-line anti-TB drugs, while essential, often exhibit higher toxicity, lower efficacy and increased costs compared to first-line medications. Managing DR-TB effectively hinges on implementing tailored medication regimens guided

Table 2: Description of Newer Anti-microbial agents used in TB.[44-46]

Class of Anti-microbial agents	Drug	Description
Diarylquinolines and Respiratory chain inhibitors	Bedaquiline	Bedaquiline is an innovative antitubercular medication that belongs to the diarylquinoline class. The medication inhibits ATPase function specifically and selectively. Mycobacterial strains that are hibernating or reproducing exhibit this restriction. An F0F1 ATP synthase component, the rotor ring, is the target of an antitubercular drug. Drug bonding to the synthase's c subunit takes place. Ongoing work is being done to create diarylquinolines of a second generation, though. The use of medications has been linked to improvements in cardiac liability.
	Telacebec Q 203	A chemical with imidazopyridine antitubercular properties that specifically targets the cytochrome b subunit (QcrB) within the cytochrome bc1 complex within the Electron Transport Chain (ETC). Additionally important to ATP production is the complex. While the medication is present, intracellular ATP is rapidly depleted and ATP homeostasis is disturbed in dormant Mtb. Compared to Bedaquiline, the results show greater promise.
Fluroquinolones	Gatifloxacin	A crucial stage of chromosomal replication is stopped by gatifloxacin, which also inhibits DNA gyrase in the same way as moxifloxacin.
	Moxifloxacin	This medication is a broad-spectrum 8-methoxy fluoroquinolone. Both Gram-positive and Gram-negative bacteria are susceptible to the drug's bactericidal effects. Prokaryotic bacterial DNA gyrase is inhibited inactivated as the action mode.
Inhibitors of MnpL (*Mycobacterial* membrane protein Large)	SQ 109	SQ 109 has a strong effect on latent cells that do not synthesize cell walls and bacteria and fungi that lack mycolic acids. A thorough understanding of SQ 109's mode of action has shown that it prevents the generation of ATP, menaquinone and cells from respiring. SQ 109 is a viable and efficient therapeutic candidate for treating multidrug-resistant tuberculosis due to its broad use.
InhA inhibitors	Isoniazid	The mainstay of therapy for TB is isoniazid. Reductase enoyl Isoniazid targets the *Mycobacterium* InhA at the molecular level. Mycolic acid production, a characteristic of the outer cell wall of mycobacteria, depends on InhA and is required for the proliferation and pathogenicity of the organism.

by drug susceptibility testing results. Early detection of DR-TB is crucial for timely treatment initiation. Bedaquiline and delamanid are commonly used as last-resort treatments for Multidrug-Resistant (MDR) TB, yet their severe side effects and emerging resistance highlight the urgent need for novel drugs and treatment approaches. The development of 19 new drug regimens offers promise in simplifying treatment protocols by eliminating the need for current drug susceptibility testing requirements. Recent international efforts in TB treatment underscore evolving strategies in combating the disease.[52-54] A few new anti-TB and repurposed drugs are under clinical development[50] as shown in the pipeline as shown in Table 3.

INDIA OVERCOMING FROM TB BEFORE 2030: A ROADMAP

A rise of Tuberculosis in India: In 2021, an estimated 504,000 individuals in India lost their lives to Tuberculosis (TB), equating to nearly one death every minute. India bears the burden of over a quarter of the global TB cases. In 2018, The United Nations committed to eradicating the epidemic worldwide by 2030 through the "End TB" strategy, aiming for an 80% reduction in TB incidence and a 90% decrease in deaths, while also eliminating financial burdens on households affected by TB. India took a step further by setting a goal to eliminate TB within the country by 2025, 5 years ahead of the UN's target. However, a recent survey, the first of its kind since the 1950s, revealed that TB rates in the Indian population are much higher than expected. The initial national tuberculosis survey in India, conducted from 1955 to 1958, reported an average of 4 out of every 1,000 people having TB. After this, the establishment of the National Tuberculosis Institute in 1959 led to a comprehensive research effort by a diverse group of experts. This culminated in the creation of the NTP in 1963, with the primary strategy being the use of chemotherapy for treatment. Despite these efforts, the recent findings indicate a need for renewed and intensified approaches to address the persistent challenges posed by TB in India.[54]

Table 3: Newer anti-TB agents and repurposed drugs under clinical development.[46]

Development Status	Stage/ Phase	Anti-TB agents
Discovery	Lead Optimization	PanD inhibitors
		Diarylthiazoles
		DprE1 inhibitors
		Indazole sulfonamides
		Macrolide Gyrase inhibitors
		Translocase-1
Preclinical Development	Early-Stage Development	JSF-3285*
		NTB-3319*
		TB-47*
		MPL-446, 447*
		CPZEN-45*
		TZY-5-84*
		FNDR-20081*
		Spectinamide-1810*
	GMP/GLP Toxicity	GSK-839*
		OTB-658
		Sanfetrinem
Clinical Development	Phase 1	BVL-GSK098*
		Macozinone*
		TBAJ-587
		TBI-223
		TBI-166
		GSK-286*
	Phase 2	SPR720*
		BTZ-043*
		TBA-7371*
		Delpazolid
		Sutezolid
		Telacebec*
		SQ-109*
		Macozinone*
	Phase 3	Badaquiline*
		Delamanid*
		Pretomanid*

Steps taking forward to eradicate TB from India: The recently published results of the latest national TB survey in India (2019-21) reveal that slightly over 3 individuals per 1,000 have active cases. This represents a modest improvement compared to the earlier survey conducted in the 1950s, which reported a rate of four per 1,000. However, it is notably higher than the World Health Organization's (WHO) 2020 estimate of 1.8 per 1,000. The city with the highest prevalence is Delhi, where the rate surpasses five per 1,000. Certain demographic groups exhibit a higher prevalence of TB, including the elderly, malnourished individuals, smokers, those with alcohol dependence and diabetics. Despite efforts over the years, the persistence of relatively high TB rates emphasizes the ongoing challenges in combating the disease in India. India's National Strategic Plan for Tuberculosis Elimination outlines a comprehensive approach based on four strategic pillars: Detect, Treat, Prevent and Build (DTPB). The "Detect" pillar emphasizes the early identification of potential TB cases at the initial point of care, followed by prompt diagnosis utilizing highly sensitive diagnostic tests. The "Treat" aspect involves the initiation and consistent administration of first-line anti-tuberculosis drug treatment for patients with drug-sensitive TB, along with appropriate antibiotics for those with drug- resistant TB. Under the "Prevent" pillar, efforts focus on expanding airborne infection control measures in healthcare facilities, providing treatment for TB infection among contacts of confirmed cases and addressing social determinants such as crowded living conditions and sanitation. Lastly, the "Build" component aims at reinforcing and enhancing the existing health services to prevent and treat tuberculosis, while also advocating for a higher priority for TB within the broader health and development agenda.[55]

CONCLUSION

The treatment of tuberculosis necessitates a coordinated, interdisciplinary strategy that includes early detection, efficient therapy, preventative measures and ongoing research. We can lessen the impact of this long-standing illness and get closer to our goal of a TB-free world with persistent commitment and investment. Comprehensively combating the TB epidemic depends on international cooperation and finance. Supporting research, diagnosis, treatment and preventive initiatives requires collaboration between international organizations, governments and non-governmental organizations, especially in areas with a high TB burden.

Hope for more efficient management has recently been raised by improvements in TB research and healthcare infrastructure. The creation of novel medications holds promise for the treatment of drug-resistant TB. Furthermore, work on a TB vaccine and diagnostic methods is still being done.

Governments, healthcare professionals and communities must work together consistently if they are to succeed in eliminating TB as a hazard to the public's health. More efficient management has recently been raised by improvements in TB research and healthcare infrastructure. The creation of novel medications holds promise for the treatment of DR TB. Furthermore, work on a TB vaccine and novel diagnostic methods is still being done.

ACKNOWLEDGEMENT

The authors extend the sincere gratitude to Amity Institute of Pharmacy, AUUP, Lucknow campus for providing an enriching academic environment that has nurtured the scholarly pursuits and facilitated our research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATP: Adenosine triphosphate; **COVID-19:** Corona virus disease 2019; **DNA:** Deoxy ribonucleic acid; **DR-TB:** Drug resistance tuberculosis; **DTPB:** Detect – Treat – Prevent – Build; **GMP/GLP:** Good manufacturing practices/Good laboratory practices; **HIV/AIDS:** Human immunodeficiency virus & acquired immune deficiency syndrome; **LAM:** Mycobacterial lipoarabinomannan; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **NTP:** National tubercular programme; **RNA:** Ribonucleic acid; **WHO:** World health organisation.

REFERENCES

1. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. Bull World Health Organ. 1992;70(2):149-59.
2. Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk factors associated with default among new smear positive TB patients treated under DOTS in India. PLoS ONE. 2010;5:43. doi: 10.1371/journal.pone.0010043.
3. Coscolla M, Gagneux S, Menardo F, *et al.* Phylogenomics of *Mycobacterium africanum* reveals a new lineage and a complex evolutionary history. Microb Genom. 2021;7. DOI:10.1099/mgen.0.000477.
4. Erramilli A, Narreddy S, Anisetti R, Grace A, Rakuditti S. Patient's perceptions of barriers to tuberculosis care in private sector in India. In Open Forum Infect Dis. 2019;6:2019. doi: 10.1093/ofid/ofz360.1236.
5. Chee CBE, Reves R, Zhang Y, *et al.* Latent tuberculosis infection: opportunities and challenges. Respirology. 2018;23:893-900.
6. Churchyard G, Kim P, Shah N. S., Rustomjee, R. Rustomjee, Gandhi N, Mathema B. M, *et al.* What We Know About Tuberculosis Transmission: An Overview J Infect Dis, 2017;216(suppl_6):S629-35, https://doi.org/10.1093/infdis/jix362
7. Cohen A, Mathiasen VD, Schon T, *et al.* The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2019;54:1900655.
8. Types of TB drug-resistance. World Health Organization. https://www.who.int/teams/global-tuberculosis-programme/diagnosis treatment/treatment-of-drug-resistant-tb/types-of-tb-drug-resistance#:~:text=Types%20of%20drug%2Dresistant%20TB&text=Rifampicin%20resistanc %20(RR)%3A%20resistance,%2Dresistance%2C%20MDR%20or%20XDR.
9. Conradie F, Diacon AH, Ngubane N, *et al.* Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382:893-902.
10. S. Tiberi, E. Pontali, M. Tadolini, L. D'Ambrosio, G.B. Migliori, Challenging MDR-TB clinical problems-The case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs, Int J Infect Dis, 2019;80:S68-72.
11. Munoz L, Stagg HR, Abubakar I. Diagnosis and management of latent tuberculosis infection: table 1. Cold Spring Harb Perspect Med. 2015;5:a017830.
12. Ahmad, N., Ahuja, S. D., Akkerman, O. W., Alffenaar, J. C. anderson, L. F., Baghaei, P., *et al.* Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: An individual patient data meta-analysis. Lancet. 2018;392(10150):821-34. doi:10.1016/S0140-6736(18)31644.
13. Ketema W, Woubishet K, Tesfaye S, Gutema S, Taye K, Shibeshi MS, Tagesse N. A Breakthrough in the Challenges of Tuberculosis Diagnosis: Lateral Flow Urine Lipoarabinomannan (LAM) Assay for the Diagnosis of Active Tuberculosis in a Subset of Human Immuno Deficiency Virus (HIV) Patients at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia. Int Med Case Rep J. 2022;15:393-7. https://doi.org/10.2147/IMCRJ.S373197
14. Abdelwahab M. T, Court, R., Everitt, Diacon D, Dawson A. H, Svensson R, E. M., *et al.* Effect of clofazimine concentration on QT prolongation in patients treated for tuberculosis. Antimicrob. Agents Chemother. 2021;65(7):e0268720. doi:10.1128/AAC.02687-20
15. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, *et al.* A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. Nat Med.
16. World Health Organisation. Tuberculosis, (2020, accessed 17 September 2020). https://www.who.int/news-room/fact-sheets/detail/tuberculosis
17. Ministry of Health & Family Welfare-Government of India https://tbcindia.gov.in/index1.php?lang=1&level=1&sublinkid=4571&lid=3176
18. Himachal Pradesh State Report, Retrieved 1 July 2023 from https://www.nhm.gov.in/images/pdf/nrhm-in-state/state-wiseinformation/himachal pradesh/hp_report.pdf
19. Neema V. Tuberculosis diagnostics: Challenges and opportunities. Lung India. 2012;29(3):259-66. doi: 10.4103/0970-2113.99112.
20. Singh S, Dey B, Sachdeva KS, Kabra SK, Chopra KK, Chaudhary VK, *et al.* Challenges in tuberculosis diagnosis and management: recommendations of the expert panel. J Lab Physicians. 2015;7(1):1-3. doi: 10.4103/0974-2727.154778.
21. MacGregor-Fairlie M, Wilkinson S, Besra G.S, Oppenheimer P.G; Tuberculosis diagnostics: overcoming ancient challenges with modern solutions. Emerg Top Life Sci. 2020;4(4):435-48. doi: https://doi.org/10.1042/ETLS20200335
22. Böncüoğlu, Elif MD; Akaslan Kara, Aybüke MD; Bayram, Nuri MD; Devrim, İlker MD; Kiymet, Elif MD; *et al.* A Diagnostic Challenge Is it Tuberculosis?. The Pediatric Infectious Disease Journal. 2022;41(5):e254. doi: 10.1097/INF.0000000000003485.
23. Chikovani I., Diaconu K., Duric P. *et al.* Addressing challenges in tuberculosis adherence via performance-based payments for integrated case management: protocol for a cluster randomized controlled trial in Georgia. Trials. 2019;20: 536. https://doi.org/10.1186/s13063-019-3621-z
24. Nunemo MH, Gidebo KD, Woticha EW, Lemu YK. Integration Challenges and Opportunity of Implementing Non-Communicable Disease Screening Intervention with Tuberculosis Patient Care: A Mixed Implementation Study. Risk Manag Healthc Policy. 2023;16: 2609-33.https://doi.org/10.2147/RMHP.S432943
25. Pradipta IS, Idrus LR, Probandari A, *et al.* Barriers and strategies to successful tuberculosis treatment in a high-burden tuberculosis setting: a qualitative study from the patient's perspective. BMC Public Health. 2021;21: 1903. https://doi.org/10.1186/s12889-021-12005-y
26. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, *et al.* A patient-level pooled analysis of treatment-shortening regimens for drug- susceptible pulmonary tuberculosis. Nat Med.
27. Middlebrook G 1954 Isoniazid resistance and catalase activity of tubercle bacilli. Am Rev Tuberc65:471- 472
28. Kundu S Marzan M. Gan S.H. Islam M.A. Antibiot (Basel). Prevalence of antibiotic-resistant pulmonary tuberculosis in bangladesh: asystematic review and meta-analysis. 2020;9, https://doi.org/10.3390/antibiotics9100710
29. Banerjee A, Dubnau E, Quemard A, *et al.* inhA, a gene encoding a target for isoniazid and ethionamide in *Mycobacterium tuberculosis*. Science. 1994;263:227-30.
30. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, *et al.* Guidelines for the treatment of latent tuberculosis infection: recommendations from the national tuberculosis controllers association and CDC, 2020. MMWR Recomm Rep, 2020;69(1):1-11.
31. Centers for Disease Control and Prevention. User Guide: Molecular Detection of Drug Resistance (MDDR) in *Mycobacterium tuberculosis* Complex by DNA Sequencing (Version 3.0). 2023. Available at: https://www.cdc.gov/tb/ topic/laboratory/mddr user-guide.htm. Accessed 5 March 2023.
32. Tiberi S, Pontali E, Tadolini M, D'Ambrosio L, Migliori G.B, Challenging MDR-TB clinical problems-The case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs, Int J Infect Dis, 2019;80:S68-72.
33. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, *et al.* Bedaquiline- Pretomanid-Linezolid regimens for drug-resistant tuberculosis. N Engl J Med. 2022;387:810-23.
34. Agyemann, A.A.; Ofori-Aseno, R. Efficacy and safety profile of linezolid in the treatment of multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis: A systematic review and meta- analysis. Ann Clin Microbiol Antimicrob. 2016:15.
35. Piddock LJ. Fluoroquinolone resistance: overuse of fluoroquinolones in human and veterinary medicine can breed resistance. BMJ. 1998;317(7165):1029-30. doi: 10.1136/bmj.317.7165.1029.
36. Smoskovi, A., Parsons, L.M. Salfinger, M. The molecular basis of resistance to isoniazid, rifampin and pyrazinamide in *Mycobacterium tuberculosis*. Respir Res. 2001;2:164. https://doi.org/10.1186/rr54
37. Kambli P, Ajbani K, Nikam C, Sadani M, Shetty A, Udwadia Z, *et al.* Correlating rrs and eis promoter mutations in clinical isolates of Mycobacterium tuberculosis with phenotypic susceptibility levels to the second-line injectables. Int J Mycobacteriol. 2016;5(1):1-6.
38. Bloemberg GV, Keller PM, Stucki D, Trauner A, Borrell S, Latshang T, *et al.* Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. N Engl J Med. 2015;373(20):1986-8.
39. Saeed A, Ali H, Yasmin A, Baig M, Ullah A, Kazmi A, *et al.* Unveiling the Antibiotic Susceptibility and Antimicrobial Potential of Bacteria from Human Breast Milk of Pakistani Women: An Exploratory Study. BioMed Res Int. 2023;6399699.

40. Sufyan M, Daraz U, Hyder S, Zulfiqar U, Iqbal R, Eldin SM, *et al.* An overview of genome engineering in plants, including its scope, technologies, progress and grand challenges. FunctIntegr Genomics. 2023;23(2):119.
41. O'Brien RJ, Nunn PP. The need for new drugs against tuberculosis: obstacles, opportunities and next steps. Am J Respir Crit Care Med. 2001;163(5):1055
42. Mitchison DA. Shortening the treatment of tuberculosis. Nat Biotechnol. 2005;23(2):187-8.
43. Mohite P, Nahar D, Pawara R, Alqahtani T, Eldin SM, Mukerjee N, Al-Tawaha AMS, Iqbal R, Bawazeer S, Ali I. Triazolopyridine, a leitmotif of synthetic methods and pharmacological attributes: an extensive review. Arab J Chem. 2023;16.
44. van den Boogaard J, Kibiki GS, Kisanga ER, Boeree MJ, Aarnoutse RE. New drugs against tuberculosis: problems, progress and evaluation of agents in clinical development. Antimicrob Agents Chemother. 2009;53(3):849-62.
45. Kumar R, Takkar P. Repositioning of Isatin hybrids as novel anti-tubercular agents overcoming pre-existing antibiotics resistance. Med Chem Res. 2021;30:847-876.
46. Dasgupta R, Seeberg J. India planned to eliminate TB by 2025, but it's estimated half a million Indians are still dying from it every year. The Conversation Global. 2022.
47. Karakousis P, Parry Z, Klinkenberg L, Pinn M, Nuermberger E, Grosset J. Towards establishing a high-burden guinea pig model for TB chemotherapy, abstr. 11. Abstr. 1st Int. In Workshop Clin. Pharmacol.; Tuberc. Drugs, Toronto, Canada, 2008.
48. Sharma A, De Rosa M, Singla N, Singh G, Barnwal RP, Pandey A. Tuberculosis: an overview of the immunogenic response, disease progression and medicinal chemistry efforts in the last decade toward the development of potential drugs for extensively drug-resistant tuberculosis strains. J Med Chem. 2021;64(8):4359-95.
49. De Groote MA, Huitt G. Infections due to rapidly growing mycobacteria. Clin Infect Dis. 2006;42(12):1756-63.
50. Serpi M, Ferrari V, Pertusati F. Nucleoside-derived antibiotics to fight microbial drug resistance: new utilities for an established class of drugs? J Med Chem. 2016;59(23):10343-82.
51. Van Heeswijk RPG, Dannemann B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug-drug interactions. J AntimicrobChemother. 2014;69(9):2310-8.
52. Kroesen VM, Gröschel MI, Martinson N, Zumla A, Maeurer M, van der Werf TS, Extraauthor. Non-steroidal anti-inflammatory drugs as host-directed therapy for tuberculosis: a systematic review. Front Immunol. 2017;8:772.
53. Dooley KE, Rosenkranz SL, Conradie F, Moran L, Hafner R, von Groote-Bidlingmaier F, *et al.* QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomized, controlled trial. Lancet Infect Dis. 2021;21(7):975-983.
54. Sachan RS, Mistry V, Dholaria M, Rana A, Devgon I, Ali I, *et al.* Overcoming *Mycobacterium tuberculosis* drug resistance: novel medications and repositioning strategies. ACS omega. 2023;8(36):32244-57.
55. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med. 2013; 2013:828939. doi: 10.1155/2013/828939. Epub 2013 Feb 12.
56. Chiratidzo R. Chamboko, Wayde Veldman, Rolland Bantar Tata, Birgit Schoeberl, Özlem Tastan Bishop. Human Cytochrome P450 1, 2, 3 Families as Pharmacogenes with Emphases on Their Antimalarial and Antituberculosis Drugs and Prevalent African Alleles. International Journal of Molecular Sciences. 2023;24(4): 3383.https://doi.org/10.3390/ijms24043383
57. Barry CE 3rd, Slayden RA, Mdluli K. Mechanisms of isoniazid resistance in *Mycobacterium tuberculosis*. Drug Resist Updat. 1998;1(2):128-34. doi: 10.1016/s1368-7646(98)80028-9.
58. David HL. Probability distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculosis*. Appl Microbiol. 1970;20(5): 810-4.

Cite this article: Srivastava V, Verma A. Current Challenges in the Management of Tuberculosis. J Young Pharm. 2024;16(2):145-54.