Multidrug-Resistant Tuberculosis: Challenges and Solutions

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Abstract

Multidrug-Resistant Tuberculosis (MDR-TB) has become a major global health challenge because there is limited scope of treatment options when rifampicin and isoniazid - two frontline drugs in standard TB treatment regiments are resistant. This resistance significantly impairs the effectiveness of present therapies and prolongs the time it takes to treat, increasing the cost burden and mortality rates in afflicted populations. Intrinsic drug resistance, formation of nonreplicating bacilli, poor vascularization of granulomatous lesions, poor clinical agent management, and genetic mutations of Mycobacterium tuberculosis genes are MDR-TB resistance mechanisms. As these factors complicate treatment outcomes, new types of interventions are needed to overcome barriers. Diagnostical tools and therapeutic strategies have also been advanced, including new drugs, combination regimens and new molecular diagnostic methods all have promising solutions. However, solutions to the treatment challenges need to be developed to address rapid diagnostics, effective drug delivery, and improved patient adherence. There is a need to find more sustainable and innovative ways to manage and successfully treat MDR-TB.

Keywords: Types of resistance, MDR-TB, Treatment challenges, Novel Approaches

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Introduction

Advances in multidrug-resistant tuberculosis (MDR-TB) are part of the history and the rising antibiotic resistance to tuberculosis (TB) treatment. For centuries tuberculosis has affected humans, proof of which exists as far back as 2400 BCE (Dheda et al., 2024). MDR-TB emerged after antibiotics revolutionized TB care with streptomycin in the year of 1944. Then in 1946, PAS and isoniazid in 1952 followed by rifampicin in 1965. These drugs facilitated effective treatment regimens, but improper use caused drug resistance. MDR-TB was evident by the 1960s and resistance to individual drugs. By the 1980s it was becoming a global concern. This highlights the essential need for proper TB treatment to prevent resistance. Multidrug-resistant TB (MDR-TB) was recognized as a global threat in the 1980s. It arises when *Mycobacterium tuberculosis* becomes resistant to isoniazid and rifampicin which was the first-line anti-TB drug. Poor treatment adherence, inadequate drug supply, and improper prescribing are the primary causes (Wangnew et al., 2024).

In the early 2000s, extensively drug-resistant TB (XDR-TB) was identified as posing an even greater challenge than MDR-TB. XDR-TB became resistant to rifampicin, fluoroquinolones, and even one injectable agent like amikacin or kanamycin. Some Risk factors for TB include diabetes, weakened immunity (e.g., HIV/AIDS), malnutrition, tobacco, and alcohol usage (Sampath et al., 2023). Its treatment requires antibiotics (e.g. isoniazid, rifampicin, pyrazinamide, and ethambutol) taken daily for 4-6 months. Stopping treatment prematurely can lead to drug-resistant TB which demands alternative therapies. Proper adherence to treatment and preventive measures like vaccination are critical to controlling TB and its resistant forms (Kiziltaş & Babalik, 2023). TB remains the leading global cause of death from an infectious disease. According to WHO, in 2021 alone an estimated 10.6 million people fell ill with TB and more than 1.6 million deaths were attributed to the disease. TB, caused by *Mycobacterium tuberculosis*, can infect various body parts, including the brain, kidneys, and spine. TB infection can be classified into two types according to the level of infection. One is active TB disease and the other is latent TB infection (LTBI). The WHO estimates nearly 2 billion people globally are infected with the later one (Yadav, 2023). This chapter explores the epidemiology, challenges, and potential solutions for MDR-TB, emphasizing the urgent need for global collaboration to control and ultimately eliminate this rising threat.

Epidemiology and Global Burden of MDR-TB

Multidrug-resistant tuberculosis (MDR-TB) has been developed as a critical global health issue reporting challenges to TB control efforts.

The heavy expenses on treatment and prevention strategies cause a social and economic burden at the global level. Moreover, MDR-TB was noticed to show different burden levels according to age, sex, and region along with additional social determinants (Song et al., 2024). According to WHO Global TB reports males show higher prevalence and mortality rates from TB among most age groups. Possible reasons are smoking, alcohol abuse, and work-related stress which are commonly associated with men, and significantly increase TB risk (Bansal & Arora, 2022). Inadequate or prolonged TB treatment and drug misuse often lead to drug resistance, causing difficulties in management. Research by Zhang et al. (2023) highlights that the global TB burden primarily impacts middle-aged and older individuals (40–60 years), with age-related immune decline increasing susceptibility to MDR-TB. This study emphasizes the importance of intensified screening, early detection, and timely treatment to prevent drug resistance. It is crucial to adhere to an appropriate, combination-based, and regular medication.

In the case of region dispersal of MDR-TB, WHO reported the highest case ratios in three major countries (India, China, and Pakistan). Excessive TB incidence in these regions is linked to economic challenges and malnourished (Wardani & Wahono, 2020; Bagcchi, 2022). In addition to these, some social determinants including medicinal techniques, educational systems, occupation, and social class, cannot be neglected (Najafizada et al., 2021). However, according to population adjustment, Sub-Saharan Africa, specifically Somalia, shows an inexplicably high MDR-TB burden although it has fewer absolute cases. This region also experienced higher TB mortality rates in 2019. These findings underscore the urgent need to address MDR-TB in Africa. Effective social protection and poverty alleviation programs have shown the potential to reduce TB incidence and mortality (Nyasulu et al., 2024). Thus, these regions need to prioritize healthcare resources, combating hunger, and supporting impoverished households to reduce the MDR-TB burden.

Moreover, Joinpoint regression analysis reveals temporal trends from 1990 to 2019 which shows an initial rise in TB indicators followed by a decline after 2005 (Nehru et al., 2024). This aligns with global TB reports which noted reductions in TB deaths and incidence, while insufficient to meet the 2020 target of a 20% reduction. Despite improved treatment rates and a dropped TB burden, MDR-TB remains a significant global health threat with high mortality ratios (Sholeye et al., 2022). Hence it is necessary to concentrate on reducing drug-susceptible cases progressing to drug-resistant forms besides overall TB incidence reduction. In 2022, the WHO reported 7.5 million new TB cases as well as 1.3 million deaths marking a significant rise after disruptions caused by the COVID-19 pandemic. These disruptions led to an estimated 500,000 additional TB deaths between 2020 and 2022 (Timire et al., 2023). The WHO's End TB strategy targets a 90% reduction in TB incidence and 95% in TB deaths by 2035 (Nalunjogi et al., 2023) which was halted in 2022 by showing up of 410,000 new cases resistant to rifampicin, possessing a great challenge to drug-resistant TB control (Sanchini et al., 2024).

Treatment Challenges

Treating active TB, especially drug-resistant forms is highly challenging. Management of this disease involves prolonged use of multiple antibiotics with different drug lines for drug-susceptible TB, MDR-TB, and XDR-TB. The rise of MDR-TB highlights the need for urgent treatment strategies. Over half of global MDR-TB cases originate in India, China, and Russia, driven by incorrect dosages, incomplete treatment, and uncorrected medication errors during hospitalization (Shehzad et al., 2024). Treatment complexity also arises from disease progression variability, host immune responses, and drug resistance phenotypes. Similarly, resource-limited countries, where TB is most prevalent encounter additional challenges due to healthcare infrastructure that supports only basic interventions.

The WHO's 2016 recommendation for intense chemotherapy regimens along with TB drugs reflects the necessity of comprehensive treatment frameworks. Additionally, the resistance due to chromosomal mutations further emphasizes the importance of advanced molecular diagnostics to enhance treatment precision and outcomes (Migliori et al., 2020). Some factors involved in treatment challenges are discussed below.

Type of Drug-Resistant Mechanism in TB

Bacteria have a remarkable genetic plasticity that permits them to fight a wide range of environmental threats along with the residence of antibiotic molecules which can endanger their existence, according to previous reports (Kraemer et al., 2019). Drug resistance in TB evolved through two major pathways. One is known as the primary pathway, which occurs when an individual is infected with a strain already resistant to TB drugs, making standard treatments ineffective (Hlanze et al., 2024). However, the novel drug and combined drug can potentially treat this resistance. The second is Acquired resistance pathway, which develops when a susceptible strain undergoes mutation due to inadequate treatment. This resistance can arise through mutations in antimicrobial targets, drug uptake mechanisms, efflux systems, or metabolic pathways. Due to the emergence of resistant strains treatment failure occurs (Aslam et al., 2024). Other key factors contributing to multi-drug resistance in TB include poor patient adherence, physician errors, inadequate granuloma vascularization, intrinsic resistance of Mtb, the formation of non-replicating bacilli, and mutations in Mtb genes (Wamalwa et al., 2024). The mechanism of action of antibiotics on bacterial cells is shown in Figure 1.

Errors in Management for the Treatment of MTB

The most challenging factor for the treatment of MtB is the management faults. It is often caused by some human factors and carelessness that leads to poor outcomes. According to studies and research, the main reasons for these errors are the lack of trained healthcare providers, inadequate treatment protocols, insufficient patient education, and poor monitoring of treatment progress (Singha et al., 2024). Additionally, challenges like inadequate drug supply, poor storage settings, and incorrect dosing delay the effective treatment. Moreover, some patient-related issues such as lack of treatment knowledge, adverse drug effects, and malabsorption further complicate the response to therapy (Datta et al., 2024). These factors collectively contribute to the rising frequency of drug-resistant TB.

Complexity of TB Granulomas

Tuberculosis (TB) presents a complex pathology with treatment taking months to a year due to the heterogeneous granulomatous

lesions present in both active and latent forms of the disease. These lesions vary from well-vascularized granulomas containing neutrophils and macrophages to avascular caseous granulomas with necrotic centers caused by host cell lysis and bacterial activity (Song et al., 2024). The tubercle bacilli within these lesions exist in different stages, from actively replicating (AR) bacilli in vascularized granules to slowly replicating (NR) bacilli in avascular caseous granules. According to experimental studies on animals, drugs like PZA, RIF, INH, and EMB are effective against intracellular AR bacilli, but they are less effective against extracellular NR bacilli (Weeratunga et al., 2024). Drug resistance may develop due to temporal and spatial variations in drug distribution as well as the enlargement of caseous granulomas that can form pulmonary cavities. These cavities contain both intracellular and extracellular bacilli which rapidly multiply when exposed to oxygen resulting in increased bacterial load and the potential for mutations that confer resistance to frontline TB drugs (Malherbe et al., 2024).

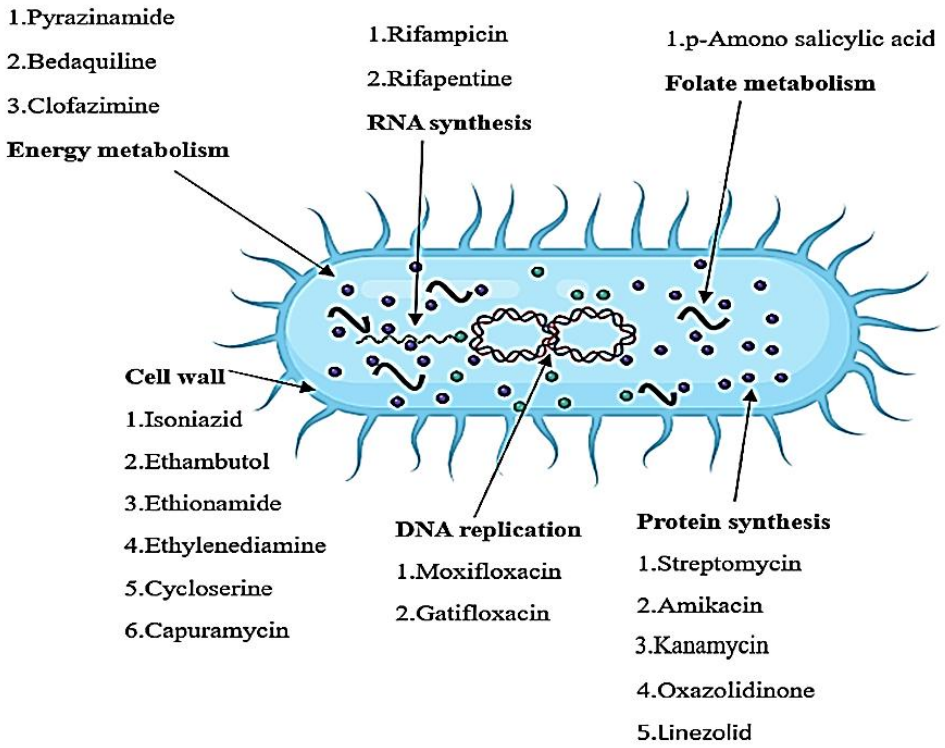

Fig. 1: Mechanism of action of antibiotics on bacterial cell

Intrinsic Drug-Resistance of MTB

Drug Resistance is the major emerging issue which needs serious attention (Abbas et al., 2025). Mycobacterium tuberculosis (Mtb) has evolved several intrinsic mechanisms such as degradation of drugs, and target variations, to resist antibiotics that allow it to thrive in hostile environments (Singha, et al., 2024). These mechanisms include modifications to the cell envelope, efflux pumps, and other cellular processes that contribute to drug resistance (Eoh et al., 2024). The mycobacterial cell envelope is complex, consisting of long-chain mycolic acids (MA), peptidoglycan (PG), arabinogalactan (AG), and a lipid-rich outer membrane. The structure of this envelope prevents the penetration of hydrophilic antibiotics in order to make Mtb naturally resistant to many drugs (Nan et al., 2024). For example, first-line TB drugs like isoniazid (INH) inhibit MA synthesis, and ethambutol (EMB) targets AG synthesis (Chowrasia et al., 2024). However, the layers of AG and PG act as barriers to hydrophilic molecules whereas the lipid-rich outer layer hinders the entry of hydrophobic drugs. Mutations in the cell membrane components can further enhance resistance, as seen in *Mycobacterium smegmatis*, which becomes more vulnerable to first-line drugs like rifampicin (RIF) and novobiocin when mycolate is defective (Wilhelm & Pos, 2024).

Mtb contains various efflux pumps such as members of the ATP-binding cassette (ABC) superfamily and the resistance-nodulation-division (RND) superfamily along with other families like the major facilitator superfamily (MFS), small multidrug resistance (SMR) family (Farnia et al., 2024). These pumps help Mtb expel a wide range of antibiotics, including INH and RIF. Mtb can upregulate efflux pump genes when it is exposed to sub-inhibitory concentrations of drugs over time leading to low-level resistance. For example, overexpression of genes (*mmR EP* and *MmpL7)* has been linked to increased resistance for first-line drugs (Hasan et al., 2024).

Besides these, Mtb is also capable of developing resistance through the modification of drug targets or the production of enzymes that inactivate drugs. Mtb possesses β-lactamases which inactivate β-lactam antibiotics and prevent their penetration across the cell membrane. Mtb also has intrinsic resistance to macrolides such as clarithromycin and azithromycin, which are mediated by an intrinsic rRNA methyltransferase that modifies ribosomal RNA inhibiting the activity of macrolides (Kaushik et al., 2024).

Phenotypical Drug-Resistance

Studies suggest that drug-resistant Mycobacterium populations, known as persisters, are phenotypically drug-resistant but genetically susceptible. These persisters are found in lung cavities and caseous granulomas of TB patients where they exhibit drug tolerance without genetic changes. They can survive drug treatment by either growing when the drug concentration is reduced or remaining dormant (Yenew

et al., 2024). Persisters are categorized into two types according to their availability. Class I (rare form) is found in replicating populations and is resistant to various drugs by different mechanisms. They can be potentially eliminated with drug combinations. On the other hand, Class II is present in most cell populations under stress conditions like starvation or hypoxia and shows resistance to many drugs. For effective treatment, there is a need for new antibiotics. Persister resistance is linked to dormancy and other stress-induced traits observed in in vitro models, such as nutrient starvation, antibiotic depletion, and hypoxia (Iacobino et al., 2020). For example, in the Wayne model, non-replicating persistent cells (NRP-2) develop a thickened outer layer that restricts drug entry, including rifampicin. According to the latest research. Some of the anti-TB drugs with the mechanism of resistance are described in Table 1.

Table 1: Types of MDR Drugs and mechanisms of resistance

Drug	Mechanism of Resistance	Cross Resistance Class	Stage	References
	First-Line Drugs			
Rifampicin	*rpoB* gene mutations reducing rifampicin binding by altering the structure of RNA polymerase β subunit. Causing a continuous bacterial-RNA synthesis despite the drug's presence.	Rifabutin, Rifapentine	MDR, XDR	(Srivastava & Verma, 2024)
Pyrazinamide	Mutations in *pncA* reduce drug activity by preventing its activation. Other mechanisms involve efflux pumps shift and mutations in *rpsA* and *panD*.	Delamanid	MDR, XDR	(Yang et al., 2024)
Isoniazid (INH)	Primarily caused by *katG* mutations to impair INH activation. Secondary mechanism includes *inhA* mutations that reduce drug binding. Mutations in other genes (e.g., ahpC, kasA) also cause drug resistance.	Ethionamide, Prothionamide	MDR, XDR	(Srivastava & Verma, 2024)
Streptomycin	Mutations in *rpsL* and *rrs* genes alter ribosomal binding sites and ultimately reduce drug efficacy.	Kanamycin, Amikacin, Capreomycin	MDR, XDR	(Xie et al., 2024)
Ethambutol	Mutations in *embB* disrupt arabinosyl transferase activity and weaken cell wall synthesis. Efflux pump systems also contribute to resistance.	Terizidone	MDR, XDR	(Yang et al., 2024)
	Second-Line Drugs			
Fluoroquinolones	Mutations in *gyrA* and *gyrB* disrupt DNA gyrase binding. Alteration of *rrs* and regulatory genes change the permeability.	-	XDR	(Olbrich et al., 2024)
Kanamycin	Resistance occurs through enzymatic modification, overexpression of efflux pumps, modifications in ribosomal sites, or production of protective ribosomal proteins.	Streptomycin, Amikacin, Capreomycin	XDR, MDR	(Srivastava & Verma, 2024)
Cycloserine	Mutations in genes for D-alanine racemase and ligase leading to lessen the binding affinity. Resistance occurs by changes in drug transport mechanisms.	-	XDR, MDR	(Moga et al., 2023)
Ethionamide	*EthA* mutations reduce drug activation while *inhA* mutations alter target binding. Efflux pumps and alternative metabolic pathways also cause resistance.	Isoniazid, Pretomanid	XDR, MDR	(Srivastava & Verma, 2024)
Para-aminosalicylic acid (PAS)	Resistance arises from mutations in *folC* (target modification) and permease genes (*iniB*, *iniC*). Efflux pumps (*iniA*, *iniB*) overexpression to reduce drug uptake and efficacy.	-	XDR, MDR	(Kay et al., 2022)
Rifabutin	Mutations in *rpoB*, efflux pump activation, and enzymatic modifications weaken rifabutin action.	Rifampicin, Rifapentine	XDR, MDR	(Moga et al., 2023)
Amikacin	Increased efflux pump systems, production of enzymes (AMEs), and ribosomal site mutations damage drug efficacy. Biofilms provide additional resistance.	Streptomycin, Kanamycin, Capreomycin	XDR, MDR	(Kay et al., 2022)
	Special/Newer Drugs			
Delamanid	*ddn* mutations reduce drug activation. Efflux pump activation lowers intracellular concentration and target alterations hinder efficiency.	Pyrazinamide	XDR, MDR	(Olbrich et al., 2024)
Bedaquiline	Efflux pump activation expels the drug leading to its resistance.	-	XDR, MDR	(Kay et al., 2022)
Pretomanid	Mutations in genes like *panD* and *fadD32*, biofilm formation, and efflux pump activation are the main mechanism of resistance.	Isoniazid, Ethionamide	XDR, MDR	(Olbrich et al., 2024)

Diagnostic Challenges

Timely diagnosis of MDR-TB is crucial for introducing an appropriate treatment. Early detection allows healthcare providers to prescribe effective regimens, restricting the risk of complications along with reducing transmission within communities. On the other hand, diagnostic delays not only prolong the infectious period but also increase the probability of severe disease outcomes and higher treatment costs. There are different diagnostic methods for *Mycobacterium tuberculosis* (Mtb) that has been evolved. The Drug Susceptibility Testing (DST) which is a phenotypic method that remains the gold standard due to its accuracy. However it generally requires a significant amount of time to deliver results (Larsson et al., 2024). The newer methods known as Rapid Diagnostic Techniques, are not only rapid and accurate but also identify chromosomal mutations. These methods include target gene sequencing, whole-genome sequencing, line probe assays, and molecular amplification technologies like the Xpert MTB/RIF system (Mousavi-Sagharchi et al., 2024).

Solutions and Methodology for Treatment for MDR-TB

Multidrug-resistant TB (MDR TB) has been a rising concern not only in developing countries but reaching quite a bit of industrialized countries in the past few years. New protocols of treatment and drug combinations are needed to address the challenge of MDR-TB (Lu et al., 2022). Recent research suggests combining novel drugs like bedaquiline and pretomanid with using vaccines or monoclonal antibodies can improve treatment outcomes (Conradie et al., 2022).

Complexity of Granuloma Formation in TB Resistance

The complexity of TB granulomas shows high significance in drug resistance. The Mtb granulomas establish a drug gradient that limits drug penetration and accounts for the resistance to Mtb. It is difficult to target these granulomas, especially in the brain (Ali et al., 2024). To be addressed better, metabolomics and proteomics can help to identify the molecular weights and characteristics of the granulomas so new drugs can be developed. The combined effect of different drugs (PZA-RIF-INH-EMB) shows more effectiveness for granulomas, especially in AR stages (Wei et al., 2024). It is therefore suggested that proteomic and metabolomic approaches should be more widely used for improving rapid diagnostic tools and treatment strategies.

Phenotypic Drug Resistance

Mtb phenotypic resistance occurs partially due to persister cells which act as reservoirs for mutation and drug resistance. This makes it important to find drugs against these dormant bacteria and turn down MDR-TB. The fact that combinations of rifapentine and rifampin at neutral pH can effectively kill persisters is shown by studies. Mtb also can be treated with other drugs (nitazoxanide and rifampin) (Dartois & Rubin, 2022).

Cell Envelope Resistance

Cell envelope resistance in Mtb is caused when mutations occur in membrane proteins like porins, which have ability to inhibit the entry of hydrophilic drugs. This challenge can sometimes be overcome by using lipophilic drugs that penetrate the waxy bacterial membrane. However, according to advanced research lipophilicity alone is not enough for drug permeability which complicates the treatment development (Sachan et al., 2023).

Improving Diagnosis

The development of rapid and accurate diagnostic tools is critical for effective control and treatment of MDR-TB as they enable early detection and timely intervention which are essential factors to prevent disease progression and transmission. Newer and more sensitive methods of diagnosis rely on using proteomics, genomics, and molecular biology to enhance sensitivity and specificity. Not only do these tools speed up the time to diagnosis but they also allow clinicians to spot drug-resistant strains for more targeted treatment regimens. The underdeveloped methods are deliberated below.

MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization Time-of-Flight)

The most rapidly adapting proteomic technique that quickly analyzes and detects proteins, aiding in the diagnosis of TB infections. It offers sensitivity and specificity ranging from 80 to 100%. The method shows the rapid process by providing results in one to four hours. However, the time depends on microbial incubation time (Ou et al., 2024).

Colorimetric Tests

These tests can detect antibiotic resistance by observing microbial growth and phenotypic changes. Although these methods are slower as they give results in 12 to 40 hours, they show high specificity (98–100%) and sensitivity (95%). These tests are useful not only for diagnosing severe but also for less severe TB cases (Reghunath et al., 2023).

FISH (Fluorescence in Situ Hybridization)

In this technique, fluorescence is used to label proteins and detect antibiotic resistance in samples. It is effective for infections with ribosomal changes caused by selective antibiotic-resistant Mtb (e.g. linezolid and clarithromycin). FISH is commonly used to test ESBLs, particularly in *Campylobacter* and *Helicobacter* species. This technique is applied to patient samples infected with multiple infections (respiratory tract infections and gastrointestinal infections). The resulting time of FISH is between 60 to 90 minutes and sensitivity ranges from 80 to 100% (Yadav, 2023).

Molecular Detection Systems

Generally, these techniques explain nucleic acids (DNA/RNA) to detect mutations associated with antibiotic resistance. They give rapid results within 1 to 3 hours and show high sensitivity ranging from 73 to 100%. These detection systems are helpful for detecting resistant strains in both health workers and colonized patients (Yang et al., 2023).

DNA Microarray

This technique screens resistance using a combination of multiple antimicrobial resistance gene markers including ESBLs and Bls in respiratory and blood specimens. Analysis takes 2.5 to 8 hours and sensitivity is 72.9% with a 2.5 to 8 hours turnaround for patients with multiple infections (Jain & Kulkarni, 2023). These diagnostic innovations are critical to faster and better detection. Consequently, advancing the development of new drugs for treating MDR-TB will need to use abundant new diagnostic tools and new drug development strategies with the growing global MDR-TB threat.

Future Directions and Research Priorities

Future research in tuberculosis (TB) treatment is focused on developing more effective drugs principally for multidrug-resistant TB. Key priorities include creating long-lasting antibacterial drugs that can be administered at extended intervals to improve patient compliance and support directly observed therapy. There is also an urgent need for compounds specifically targeting MDR-TB and drugs that can address the non-replicating (NR) or dormant stages of Mycobacterium tuberculosis (Mtb), which would be revolutionary in MDR-TB treatment. To combat drug resistance caused by efflux pumps, scientists are exploring oligonucleotide mimics and peptide nucleic acids (PNAs) for their ability to overcome resistance. Furthermore, bioinformatics, proteomics, or genomics tools hold great potential for rapidly developing 3D protein-drug models for Mtb. A sustainable production model for these drugs is necessary especially given that some may not be commercially profitable for pharmaceutical companies. Even though the new treatments are potentially effective, drug development has declined with no introduction of new drugs in over 50 years aside from those in the U.S. (e.g., rifabutin and rifapentine). The high cost and complexity of TB research alongside the challenges in developing drugs for Mtb, make this a difficult task. Preventing MDR-TB primarily involves halting the progression of regular TB into MDR-TB through early diagnosis and treatment. However, this alone is not enough. New effective drugs are critical to ensure cures and prevent further resistance. With over 50% of MDR-TB cases showing drug tolerance, the global community must act to prevent a crisis like the COVID-19 pandemic.

Conclusion

Multidrug-resistant tuberculosis (MDR-TB) remains a major global health challenge that is stimulated by inadequate treatment regimens, medication errors, and complex resistance mechanisms. The rising prevalence in high-burden countries highlights the urgency to address this issue. However, advancements in diagnostics and treatment strategies offer potential solutions. Strengthening of healthcare infrastructure, especially in resource-limited settings, and enhancing research into molecular diagnostics and targeted therapies are needed. The global community must come together and collaborate on a unified front to implement comprehensive strategies that prioritize the prevention, early diagnosis, and development of innovative treatments for MDR-TB. Only through such collaborations can successfully mitigate the growing threat of lethal disease and safeguard public health on a global scale. As a result, it will ensure that future generations are not burdened by the devastating consequences of this deadly disease.

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