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Cover Page Footnote

The authors extend their gratitude to Dr. Dev Kumar Shah (Trinity Medical Sciences University, St. Vincent and the Grenadines), Dr. Sabin Kumar Ranabhat (Xavier University School of Medicine, Aruba, Dutch Caribbean), and Dr. Puja Neupane (IU Health Pathology Laboratory, Indianapolis, Indiana, USA) for their valuable reviews and constructive feedback.

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Review Article

MUTATIONS AND ANTIBIOTIC RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS*

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ABSTRACT: *Mycobacterium tuberculosis* (MTB) is a bacterium known to target, infect, and destroy lung cells as well as connective tissues within the body. This bacterium is prevalent worldwide and has infected over a quarter of the current world population, becoming one of the most successful pathogens in history. Due to its extreme transmission rates as an airborne pathogen, MTB strains have been treated with antibiotics such as rifampicin and isoniazid, which inhibit bacterial infection in the human body. These first-round drugs remained as successful mechanisms for slowing and killing the pathogen, notably through rifampicin's inhibition of RNA-polymerase and isoniazid's ability to halt the formation of the bacterial cell wall. However, TB has proven a threat due to the recent discovery of multi-drug-resistant tuberculosis strains, rendering these first-round drugs ineffective. The major objectives of the present study were to 1) review the most recent published literature on TB, 2) examine the role of mutations on antibiotic resistance in TB strains and 3) share our synthesis on the successes and challenges of TB treatment worldwide. Our research was guided through data available in the NCBI GenBank, and a review of literature. To accomplish these objectives, we reviewed relevant literature on *Mycobacterium tuberculosis* to collect pathophysiological data, trends in TB mutations, and present-day applications of how this disease is continually prevalent worldwide. We collected antibiotic responsive *rpo*B gene sequences from the National Library of Medicine's GenBank to assess mutations specific strains of TB from four countries. We found that random mutations caused the evolution of TB strains with effective antibiotic resistance and the selective nature of the medications encourages these antibiotic-resistant genes. New medications, like bedaquiline, take considerable research but effectively find new druggable targets against these resistant mycobacteria. However, MDR TB still remains a considerable threat despite some newly developed drugs.

Key Words: *Mycobacterium tuberculosis*, antibiotic resistance, tuberculosis, *Mycobacterium tuberculosis rpo*B gene mutation, and matrix metalloproteinases

INTRODUCTION

Mycobacterium is characterized by its mold-like growth pattern, hence the name *Mycobacterium* or "fungi bacterium" [1]. *Mycobacterium tuberculosis* (MTB) primarily targets the plasma membrane of lung cells and causes disease through manipulating natural proteasomes called matrix metalloproteinases (MMPs) [1]. These proteasomes, which typically exist in low concentrations, are crucial for breaking down specific proteins to remodel or repair cells. In individuals infected by tuberculosis, higher levels of MMPs are detected, particularly MMP-1 degrading collagen, and MMP-9 that breaks down extracellular matrix proteins, severely impacting the lungs' function especially resulting in hypoxia [2, 3]. This destruction of lung structure drastically harms its ability to diffuse gases. This remodeling effect can also lead to small, inflamed areas of white blood cells called granulomas [1]. This process is mediated by a type IV hypersensitivity reaction, also known as a delayed-type hypersensitivity (DTH) reaction [4]. The granulomas, unable to handle the necrosis of TB, degrade and spread the infection further, resulting in lung cavitation and eventually permanent fibrosis [5]. **Figure 1** shows how tuberculosis permanently damages lung function.

M. tuberculosis has remained a prevalent threat, ranking second highest for disease mortality rates in the world [6]. The disease has remained effective through its characteristic ability to lay dormant in an infected person for long durations. Undetected, the disease can spread quickly through airborne transmission. Eventually, the latent TB begins to attack the host's immune system causing rampant destruction if left untreated [7]. Although treatment options are available in the United States to combat TB infections, these treatments are significantly scarcer in developing countries due to diminished access to healthcare [8]. Additionally, improper sanitation practices and close-proximity living can significantly increase the chance of TB transmission [8]. Because *Mycobacterium tuberculosis* can cause extensive damage to an infected host, antibiotics are used to stop the infection from causing further damage.

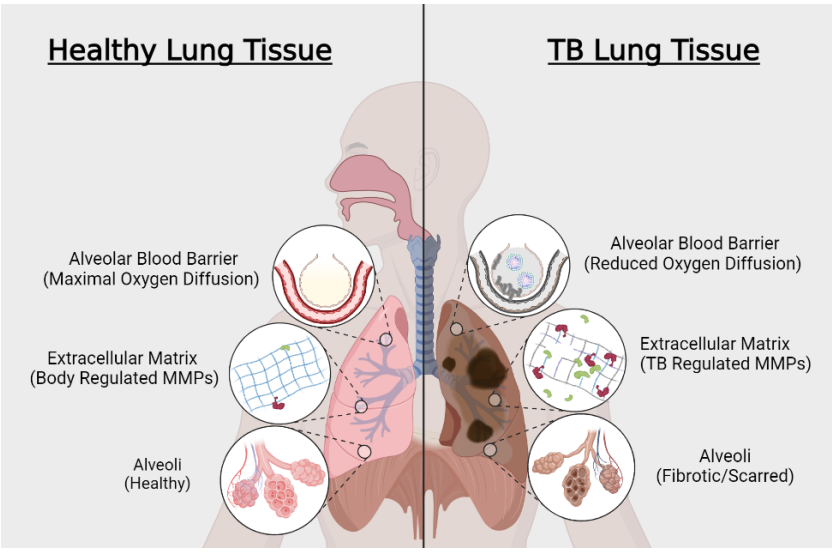

Figure 1. Tuberculosis-induced effects on the lung tissues (Figure created using BioRender)

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The infection reduces alveolar surface area, leading to hypoxia, and causes adverse effects through blockage and scarring of respiratory cells, ultimately restricting oxygen flow into the bloodstream. (Figure created using BioRender).

Rifampicin is a drug used to combat the TB strain that has been proven effective for decades. Rifampicin is an antimicrobial substance that directly inhibits DNA-dependent RNA polymerase (RNAP), preventing RNA growth at the 5′ end [9]. Because this drug has no impact on the mammalian RNAP enzyme, possible side effects are less likely to occur in humans taking the drug while still targeting the bacterial RNAP enzyme. From there, it will effectively kill the *Mycobacterium tuberculosis* within the organism by shutting down RNAP function [9]. Another common TB combatant, isoniazid, is well known for its prolonged effectiveness against TB for the past 70 years. This efficacy is due to its ability to diffuse into TB and its activation by KatG catalase-peroxidase, the bacterial defense mechanism against toxic hydrogen peroxide [10]. Once activated, isoniazid is lethal to the bacterium by preventing enzyme activation essential to the formation of the bacterial cell wall. Consequently, the TB will be destroyed within the organism without affecting the surrounding host cells due to the differentiable structures of the host cells and the bacterium [10].

Over the years, administered antibiotics have decreased the rate of TB mortalities, yet this increased use of tuberculosis-inhibiting drugs has led to drug resistance [11]. Previously, rifampicin and isoniazid were effective methods for combating TB. However, some strains of tuberculosis have developed incredible resistance to these antibiotics [11]. These strains, known as multidrug-resistant tuberculosis (MDR TB), have become a new threat to public health because of this characteristic ability. The mutated strains of TB have rapidly increased infection rates by over 20% each year [11]. Of this large percentage, only about half of all patients treated for MDR TB have a meaningful recovery [11]. Due to the dramatic effects and prevalence of MDR TB, scientific research has paved the way for advancements in antibiotic research and other treatment methods against this formidable pathogenic threat.

Original strains of TB have been difficult to analyze because mutated strains of MDR TB have become more frequent. Tissue samples are regularly used to analyze the pathophysiology of tuberculosis [12]. However, since access to these human tissues from TB infection is scarce, researchers have turned to animal tissues instead. Rabbits, guinea pigs, and mice are helpful models for observing TB pathology. However, it does not act in the exact same way as human TB [12]. Because TB studies are limited to postmortem patients of natural TB infection, some aspects of TB pathophysiology are difficult to determine based only on animal trials [12].

Scientists have developed methods to test patients for MDR TB and extensively drug-resistant tuberculosis (XDR TB) through sputum samples. The patient samples are collected and isolated in antibiotic conditions and non-antibiotic conditions. These samples are allowed to grow over a period of several weeks and analyzed at the end of the period to determine where growth occurred [13]. If growth occurred in the non-antibiotic conditions and not the antibiotic conditions, it is diagnosed as TB, but if both samples come back positive for growth, it is

probable that the patient sample contains MDR TB or even XDR TB [13]. These tests help healthcare professionals set a course of action to treat patients accurately and effectively to their disease state [13]. In recent years, molecular detection approaches have improved TB diagnosis and management. The GeneXpert MTB/RIF assay uses real-time PCR to detect Mycobacterium tuberculosis and rifampicin resistance within two hours, enhancing diagnosis speed and accuracy [14]. Line Probe Assays (LPAs) identify genetic mutations related to drug resistance in a few days, faster than traditional methods [15]. Whole-genome sequencing (WGS) offers detailed genetic insights, promising personalized treatment and better TB tracking [16]. techniques improve drug-resistant TB detection, patient outcomes, and disease control. The major objectives of the present study were 1) review the most recent published literature on TB, 2) examine the role of mutations on antibiotic resistance and 3) share our synthesis on the successes and challenges of TB treatment worldwide.

MATERIALS AND METHODS

For our research on *Mycobacterium tuberculosis*, we collected information from peer-reviewed research articles and data available in Web of Science, National Center for Biotechnology Information (NCBI) GenBank, Centers for Disease Control and Prevention (CDC), and World Health Organization (WHO) online sites to address the research objectives stated above. We aimed to explore how TB strains develop drug resistance, understand the global significance of drug-resistant TB, and examine the efficacy of various treatments for the disease over time. To understand the genetics of the drug-resistant TB bacterium, we performed a BLAST search for *M. tuberculosis rpo*B gene sequences in the NCBI GenBank database. We used a combination of keywords in the NCBI GenBank nucleotide search window: "*rpo*B *Mycobacterium tuberculosis* Ukraine", "*rpo*B *Mycobacterium tuberculosis* India", "rpoB *Mycobacterium tuberculosis* Pakistan" and "*rpo*B Mycobacterium tuberculosis China", yielding 75, 13, 9 and 10 sequences of approximately 1600 bp in length, respectively. To avoid duplication, one representative sequence from each group of identical sequences was selected for comparison, resulting in a sample size of 6 to 15 across the four countries. Thus, we acquired *rpo*B DNA sequences of TB strains from China, India, Pakistan, and Ukraine for two reasons: 1) the available sequence data were comparable in terms of length, and 2) multi-drug resistance in TB had been previously reported in these countries. After sequence acquisition, we performed multiple sequence alignment using the program MEGA to visualize mutations and construct a phylogenetic tree. Using this data, we demonstrated how different strains of TB acquired rifampicin resistance through mutations at unique genomic sites (see **Table 1**), illustrating how drug resistance can develop in various ways due to selective pressures such as antibiotics.

RESULTS

Table 1 shown below reveals mutations on the *rpoB* gene (a gene highly attributed to rifampicin resistance) from various strains of *Mycobacterium tuberculosis* from Ukraine and Pakistan, indicated by the nucleotides highlighted in pink. Strains without a pink highlight indicate an absence of mutations on that specific genomic site. Each TB strain was collected from infected

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patient samples at two different locations: Ukraine, and Pakistan. Eighteen gene sequences were aligned and analyzed using the program MEGA. While mutation sites for the samples from Ukraine were higher than those from Pakistan, genotypes were clearly country specific. Average sequence length of samples from Ukraine was 1577 bp, while it was 1673 bp for the samples from Pakistan (see **Table 2**). Genetic data clearly shows that mutation rates are highest among the TB strains from India, almost six times higher than other three countries in comparison. **Figure 2** shows the phylogenetic relationships among the TB strains from four countries. The results show that unique mutations in the *rpo*B gene can cause rifampicin resistance in tuberculosis (TB). This mutation capability of TB cells has intensified research into the drug-resistant properties of tuberculosis. Understanding these genetic changes is crucial for developing more effective treatments and combating the growing issue of drug-resistant TB.

Table 1. Mutations in the *rpo*B gene, linked to rifampicin resistance in *Mycobacterium tuberculosis* strains from Ukraine and Pakistan. While mutation sites for the samples from Ukraine were higher than those from Pakistan, genotypes were clearly country specific.

			Site #							
Origin	Organism	Strain	180	347	356	357	731	1350	1390	1532	1534
Pakistan	Mycobacterium Tuberculosis	49	C	G	C	T	C	G	T	G	T
		381	C	G	T	T	T	G	C	G	T
		408	C	G	T	T	C	G	C	G	T
		345	C	G	T	T	C	G	G	G	T
		323	C	G	T	T	C	G	C	G	T
		16	C	G	T	T	C	G	C	G	T
Ukraine		UKR97	C	G	T	C	C	G	T	T	T
		UKR96	C	G	C	C	C	G	T	G	T
		UKR95	C	G	C	C	C	G	T	G	C
		UKR94	C	G	C	C	C	G	T	G	T
		UKR78	C	G	C	C	C	G	T	G	T
		UKR77	T	G	C	C	C	G	T	G	T
		UKR76	C	G	C	C	C	G	C	G	T
		UKR69	C	A	T	C	C	T	C	G	T
		UKR68	C	G	C	C	C	G	T	G	T
		UKR67	C	G	C	C	C	G	T	G	T
		UKR28	C	G	C	C	C	G	T	G	T
		UKR27	C	G	C	C	C	G	T	G	T

Table 2. Summary of *rpo*B gene sequence characteristics and mutation rates for *Mycobacterium tuberculosis* strains from China, India, Pakistan, and Ukraine. Variations in sequence length, pairwise identity, and mutation rates are noted across the four countries.

Country	**# of Sequences**	**Sequence Length**	**Length Range**	**% Pairwise Identity**	**% Identical Sites**	**%GC**	**Average Mutation Rate** (per site)
China	10	3519	1606-3519	99.8	99.5	64.6	5.7 x10^-4
India	10	2180	1308-2180	95.2	84.4	66.3	30.0 x10^-4
Pakistan	6	1673	1673-1673	99.9	99.8	62.6	5.2 x10^-4
Ukraine	12	1577	1577-1577	99.9	99.4	62.7	4.8 x10^-4

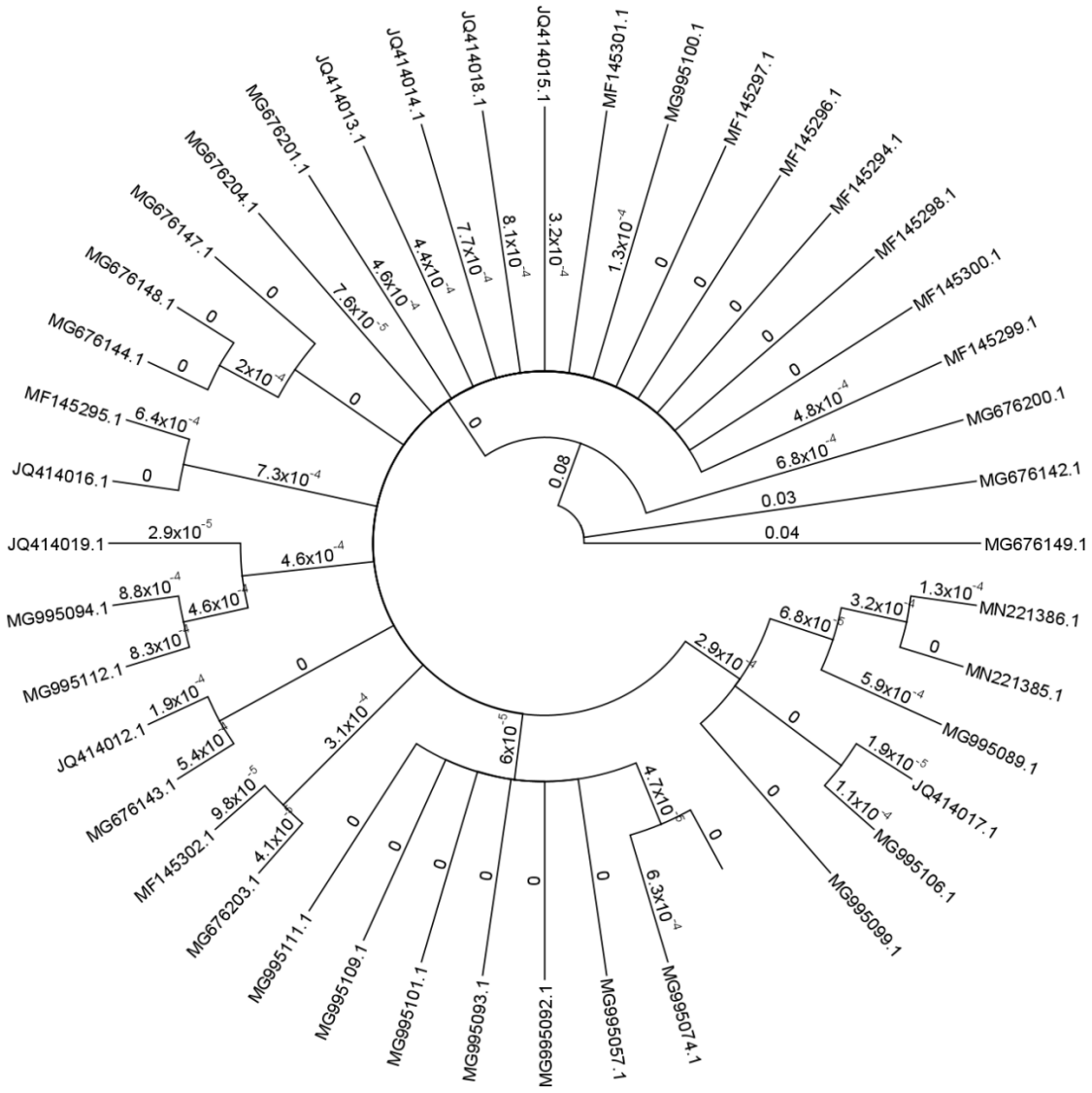

Figure 2. Maximum likelihood tree showing relationships among the TB strains from China, India, Pakistan, and Ukraine, the countries of high prevalence of TB. Phylogenetic analysis was performed using Maximum likelihood method with WAG (Whelan and Goldman) model for 500 bootstrap replications.

DISCUSSION

Overview of the Remodeling Effect and Latency of Tuberculosis—Our analysis, as shown in **Table 1** and **Figure 2**, reveals that mutations in the *rpo*B gene, associated with rifampicin resistance, vary significantly between strains from Ukraine and Pakistan. The genotypic diversity observed aligns with the higher number of mutation sites in Ukrainian strains compared to those from Pakistan. This genetic variation contributes to the remodeling effect of tuberculosis, which permanently alters lung structure and reduces oxygen diffusion efficiency, even after successful antibiotic treatment [17]. Further research into

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immunotherapeutic treatments may be needed to decrease the overall lasting damage caused by TB. When drug-resistant strains of TB are transferred to another host, they may lay dormant for long periods of time. During this period, the MDR TB is considered latent, because it is not harming the host, but is instead waiting for an opportune moment to strike. The persistence of TB in a latent state complicates tracking and treatment, as dormant strains may become active when the host's immune system is compromised or when a high accumulation of latent cells triggers an infection. This latency, driven by quorum sensing, makes TB infections challenging to detect and manage [7]. The previously described damage tuberculosis can cause is permanent in its effects. Patients in which TB is expressed often have life-long difficulties or succumb to the illness in less developed countries.

Evolution of Multidrug Resistance—Our data highlight significantly high mutation rates among TB strains from India, as seen in **Table 2** and **Figure 2**, where mutation rates are nearly six times higher compared to strains from other countries. This high mutation rate contributes to multidrug resistance (MDR TB), complicating treatment efforts. The ability of TB to evade immune detection and its rapid replication, coupled with its capacity to mutate, contributes to its prevalence in the four countries sampled in the present study and to its antibiotic resistance [18].

The causative agents of tuberculosis, grouped in the *Mycobacterium tuberculosis* complex, have infected one-quarter of the present human population as well as a wide range of other mammals. It is the 2nd most infectious leading cause of death worldwide in 2020 (the first being COVID-19), and is the 13th leading cause of death overall. Due to its effective transmissive and adaptive abilities, TB has profound consequences on developing and developed countries [6].

As original strains of TB have dissipated, new strains of TB evolved from genetic mutations [17]. MDR TB has become resistant to antibiotics once proven effective [17]. For example, as shown in Table 1, mutations in the rpoB gene site can be traced back to various strains of *Mycobacterium tuberculosis* found in Ukraine and Pakistan. This specific site, when mutated, indicates a resistance to rifampicin for that strain. While MDR TB has remained a focus of medical research in the United States, the pathogen has dramatically affected the health of millions worldwide, especially in countries with poor medical infrastructure. In the year 2013, of the over 480,000 people infected with MDR TB in Vietnam, only 97,000 began treatment due to the unavailability of effective treatment methods [17]. Similar to this influx of MDR TB cases, the issue of TB antibiotic resistance became highly prevalent following this trend worldwide [17]. Inefficacious antibiotics led to a call for new treatment methods for drugs that can inhibit the harmful effects of MDR TB [17].

During the transition from TB to MDR TB, commonly prescribed TB treating drugs were found to be ineffective for some patients [19]. Even tuberculosis antibiotics such as isoniazid and rifampicin have recently become ineffective against developing strains of MDR TB [19]. This discovery, contrary to what was once believed to be the success rate of antibiotics, has led to a surge in MDR TB research for new treatment methods [19]. Of the newly synthesized drugs,

bedaquiline (BDQ) has shown promising results to combat MDR TB [19]. This antibiotic was approved by the FDA on an accelerated track for its effectiveness and safety [19]. The BDQ drug inhibits adenosine triphosphate (ATP) synthase, the lead production mechanism of energy for the TB bacterial cell, as well as acting as a blocker for the replication of the mycobacterium [19]. Proven effective and safe in trials, the BDQ antibiotic has shown lower resistance rates in treating TB and decreased adverse effects of use [19]. Other medications like fluoroquinolones have also seen use against MDR TB. Fluoroquinolones inhibit bacterial DNA gyrase, which leads to the unraveling of bacterial DNA for use by the bacteria [19]. These medications are potent in their effects but often expensive and come with side effects to the patient. To make matter more complicated, new strains of TB are also developing resistance to these new medications. Strains resistant to rifampicin, isoniazid, bedaquiline, fluoroquinolones, and certain second-line injectables are known as extensively drug-resistant TB (XDR TB) [20].

XDR TB is thought to be a fairly rare occurrence, but has dire consequences. Considering 45% of all patients (and nearly all of HIV patients) infected with TB succumb to the disease, the prospect of an uncontrollable strain is worrying [21]. While most countries are experiencing a decrease in TB and MDR TB cases, XDR TB cases are slowly rising. From 2010-2019, XDR TB cases increased by 22.5%, with 25,060 cases worldwide [21]. It is also important to consider how global leaders in treating TB are falling short of their projected impact. The "End TB Strategy" created in collaboration with the WHO and the UN projected to decrease TB incidence and mortality by 35% in 2020 [21]. Far lower than their projections, incidence and mortality have only decreased by 11% and 9.2% respectively as of 2021 [21].

Tuberculosis Prevalence in Underdeveloped Countries—Underdeveloped countries are drastically impacted by tuberculosis spread, where high rates of HIV, poor sanitation, and limited healthcare access contribute to high infection and mortality rates [6]. As shown by our results, countries like India, and Pakistan, among others, face the highest burdens of TB. The UN's End TB Strategy aims to reduce TB incidence by 80% by 2030, but current progress falls short of this goal [8]. In contrast, developed countries like the United States have seen reductions in TB transmission, although MDR TB strains continue to pose significant challenges [22]. The high costs of treating MDR and XDR TB further emphasize the need for effective and affordable treatment options [20].

In developed countries, TB remains a prevalent threat. However, compared to developing countries where medical resources are limited, the spread of TB has shown signs of containment. According to data from 2011 to 2016, TB transmission rates reached a national low of 6.7% in the United States. Because developed countries such as the United States have more advanced treatment options, the infection rates of TB have decreased. The common forms of treatment in the United States and other developed countries include the antibiotics rifampicin and isoniazid. These antibiotics have been proven effective for several decades to treat common TB strains. Although these weaker strains of TB have decreased in transmissibility, stronger strains of TB, specifically MDR TB, have been introduced into the United States through non-residents. These strains of TB are able to surpass common antibiotic treatments and have

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become a larger threat to public health [22]. Treating resistant strains are also far more costly. During 2020 in the United States, direct treatment costs for non-MDR TB cases were $21,211 while MDR TB costs were $182,186. XDR TB, an extreme type of MDR TB, had average costs of $567,708 [20].

Recent Developments and Therapeutic Approaches— In recent years, multidrug-resistant tuberculosis has emerged as a critical topic in the medical field. As certain antibiotics lose effectiveness due to TB mutations, new treatment methods have been developed to inhibit damage caused by MDR TB in hospitalized patients [23]. In addition to newly synthesized drugs, enhanced methods of treatment have also aided in MDR TB therapeutics. One of these new methods includes the introduction of bedaquiline, which inhibits ATP synthase in TB bacteria, and delamanid, which blocks mycolic acid synthesis, both showing promising results in clinical trials [19]. Research in antibiotic resistance can positively affect the medical field by developing new alternatives to fight tuberculosis, potentially saving many lives. For instance, pretomanid, used in combination with bedaquiline and linezolid, has shown efficacy in treating highly resistant TB strains [21]. Despite these advancements, the challenges of antibiotic research are significant. Developing a new treatment method requires substantial time, financial resources, and support to conduct trials and generate data[23]. Moreover, the adaptive nature of TB bacteria means that scientists are continually engaged in a battle of natural selection. Each advancement in combating TB may eventually be met with new mutations capable of overcoming the latest medical innovations [17]. Therefore, ongoing research and development are essential to stay ahead in the fight against multi-drug-resistant TB and ensure the availability of effective treatment options.

CONCLUSION

Mycobacterium tuberculosis (MTB) continues to pose a significant threat to global public health. Its capacity to survive undetected in hosts through latency, combined with its high mutation rates, remodeling effects, and transmissibility, underscores the critical need for ongoing research and development of effective treatments, particularly in underdeveloped countries. While novel antibiotic treatments have been developed to selectively inhibit the pathogenic mechanisms of MTB, the lack of comprehensive strategies to address antibiotic resistance—stemming from incomplete treatment or improper diagnosis—poses a major challenge to control efforts. This study's examination of genetic mutations in MTB provides insights into the growing issue of antibiotic resistance, as specific mutations can render previously effective treatments ineffective. Selective pressures and the opportunity for genetic variation enable MTB to develop resistance against these antibiotics. Given the severe health consequences of MTB infection and its widespread impact, it is crucial to understand the bacterium's interactions within the host and to devise strategies to prevent antibiotic resistance. Future research could focus on analyzing MTB treatment protocols in clinical settings, evaluating treatment success rates, and investigating cases of recurrent infections. Such an approach may shed light on the persistence of MTB despite available treatments and help identify instances of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis.

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