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Pharmacological Strategies Against Mycobacterium Tuberculosis: An Overview of First-Line and Second-Line Treatments

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ABSTRACT

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health threat, with millions of new cases annually and increasing drug-resistant strains like MDR and XDR-TB. This review examines current first-line and second-line treatments, their mechanisms, targets, and resistance issues, noting that lengthy regimens, side effects, and poor adherence continue to drive resistance despite new drugs like bedaquiline, pretomanid, and delamanid showing promise yet facing accessibility challenges. Vaccine development remains crucial, as the BCG vaccine's limited protection highlights the need for innovative solutions such as mRNA and nanoparticle-based vaccines. Meanwhile, artificial intelligence (AI) is enhancing TB diagnosis and treatment monitoring, though data security and infrastructure limitations must be resolved. Achieving the WHO's End-TB goals requires a comprehensive strategy—combining better diagnostics, affordable treatments, and effective vaccines—supported by stronger healthcare systems and global cooperation to reduce TB's burden, especially in high-risk regions.

Keywords: *Tuberculosis, drug resistance, vaccines, artificial intelligence, global health.*

1. INTRODUCTION

Mycobacterium tuberculosis (Mtb), the bacterium that causes tuberculosis (TB), is a major source of illness and death worldwide. Worldwide, about one in four persons have an Mtb-induced immunological reaction disseminated by airborne droplets. This reaction could point to the development of an active illness or a dormant infection[1]. According to the World Health Organization, globally, the rise in new cases of tuberculosis (TB) that started during the COVID-19 pandemic has begun to slow. According to estimates, there were 10.8 million incident instances in 2023 (with a 95% CI of 10.1–11.7 million), a modest increase over the 10.7 million in 2022. 10.4 million instances were recorded in 2021, and 10.1 million in 2020. Most of the TB cases that occurred during 2022 and 2023 were caused by population expansion. With 134 new cases per 100,000 individuals (95% UI: 125–145), the TB incidence rate in 2023 increased by a negligible 0.2% from the year before. In 2023, 30 high-burden nations accounted for 87% of all cases worldwide, and they continue to contribute to the majority of new TB infections. Five nations accounted for 56% of the global total: China (6.8%), the Philippines (6.8%), Pakistan (6.3%), Indonesia (10%), and India (26%). Of those who contracted tuberculosis in 2023, 33% were women, 12% were children and adolescents, and 55% were men[2].

Tuberculosis infection (TBI) occurs when an individual's immune system persistently reacts to *Mycobacterium* tuberculosis (M.tb) following exposure, despite the absence of signs or symptoms of active TB disease[3]. The majority of infected individuals exhibit clinical indications or symptoms of Pleuritic chest pain, mild fever, a persistent productive cough, coughing up blood, fatigue, loss of appetite, night sweats, and unintended weight loss among the clinical symptoms of active tuberculosis[4] ,as shown in Figure 1. It is estimated that 2 billion people, or 25% of the world's population, are infected with tuberculosis (TBI), creating a sizable pool of people who could potentially become active TB patients. Individuals with weakened immune systems, including those living with HIV (PLHIV), those who are extremely young or elderly, and those who have other medical conditions, such as diabetes or malnutrition, are more likely to develop active TB. This risk can

increase to 10% annually for PLHIV[5]. The "End TB Strategy," which aims to eradicate the tuberculosis epidemic worldwide by 2035, was adopted by the World Health Assembly in 2014. A 90% reduction in new infections, a 95% reduction in TB-related mortality, and a pledge to guarantee that no family faces financial difficulty as a result of TB are among the objectives of the approach[6]. time ever, this strategy promotes the management of TBI as a crucial endeavor to reaching international goals to eradicate the tuberculosis pandemic. For this reason, the WHO revised its recommendations for TB prevention and control in 2019, intending to provide precise and useful advice for managing TB infection in both high and low-incidence This approach encourages effective TBI oversight for the first time, which is critical for achieving global goals to eliminate the tuberculosis epidemic[7].

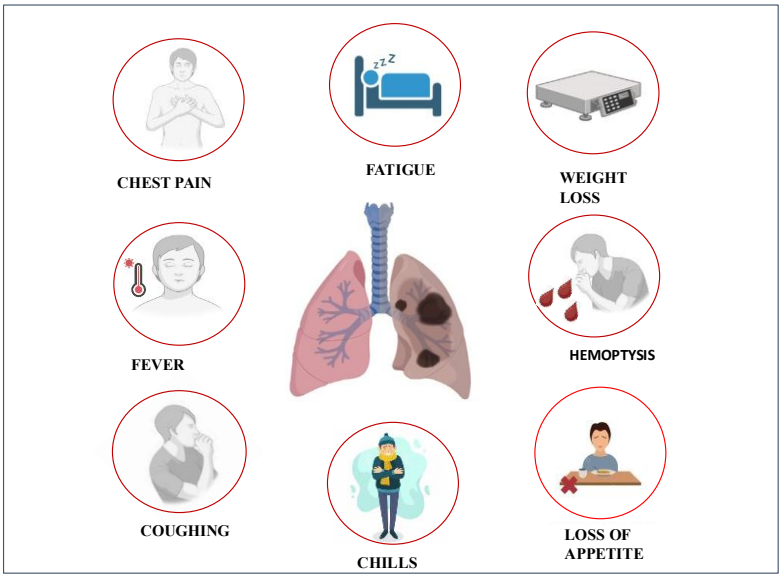

Figure 1:Signs and symptoms of active tuberculosis

Taxonomy And Description Of Genus

Mycobacterium tuberculosis is classified under

Order- Actinomycetales

Class- Actinomycetes

Family- Mycobacteriaceae

Genus- *Mycobacterium*

Mycobacterium has close phylogenetic relationships with genera like Gordonia, Tsukamurella, Nocardia, and Rhodococcus. Features and description of *Mycobacterium genus* are discussed in Table 1.

Table 1: Salient features of *Mycobacterium genus[8].*

Feature	Description
Mycobacteria	Requires oxygen for growth, does not produce spores, and lacks motility.
Shape	Rod-shaped, appearing either straight
Size	0.2-0.6 Mmby1-10 Mm
Colony Morphology	The appearance varies between species, ranging from rough to smooth textures and missing pigment to displaying carotenoid-based pigmentation.
Cell Wall	Mycolic acid (70–90 carbon atoms) is highly present in N-acetyl muramic acid, which produces acid fastness.
DNA	High G+C Content (61-71 Mol %)
Generation Time	Slow—Mycobacterium tuberculosis might take anything from 20 to 36 hours.

2. PATHOGENESIS OF MTB

The *Mycobacterium* tuberculosis complex (MTBC) has been with us for a long time, accompanying modern humans through their evolution and spreading over the planet over the past 70,000 years. TB begins its infection by entering the lungs via the respiratory system, and it is widely assumed that this bacteria can only survive and thrive inside living beings[9,10].When M. tuberculosis initially enters the body (known as a primary infection), it interacts with the lungs, as illustrated in Figure 2. Surprisingly, experts believe that its lengthy history with humans has not been a usual struggle for survival. Instead of continually fighting back and forth, as in an evolutionary weapons race, M. tuberculosis appears to have learned how to silently control the human body to help it live and spread [10]. After entering the lungs, M. tuberculosis interacts with a variety of immune cell receptors, including toll-like receptors, lectin receptors, and others located on dendritic cells and macrophages. These immune cells then take in the bacteria, which begin to proliferate inside them. Infected cells migrate to adjacent lymph nodes and use immunological signals such as TNF-α and IFN-γ to fend against germs. However, rather than halting the infection, this mechanism can assist it in expanding farther in the lung tissue, encouraging the germs to continue multiplying and migrating through the body [11] .When macrophages are activated, they emit signals that recruit more immune cells to the site of infection, causing inflammation that aids the body's defense against the invading germs. Neutrophils, another type of immune cell, are very aggressive—they can absorb germs better than macrophages and produce large numbers of reactive oxygen species, which eliminate infections through a severe oxidative attack[12] . When lymphocytes reach the infection site, they initiate a series of immunological responses. This brings in more immune cells, all working together to surround the bacteria, block it from spreading, and try to stop it from growing further[13,14].At the start of an infection, the body needs some time to activate its T-cell response. This gradual start allows the germs to settle in and establish themselves, making the infection more likely to persist[13] .The body still has a chance to eradicate the TB bacteria at this stage if the immune system is robust and functioning properly[15] .The immune system is rarely strong enough to eliminate M. tuberculosis. Instead, immune cells known as monocytes congregate around the diseased sites, forming solid clumps known as granulomas, which are a hallmark symptom of tuberculosis. To make matters worse, the bacteria may target the lung lining, causing cell death and allowing it to break through the tissue, making the infection even worse[16,17]. According to the results, controlling or halting the spread of tuberculosis depends on how the immune system responds at the actual site of infection[18] .Although granulomas are meant to keep the bacteria contained and stop it from spreading, they may inadvertently give the bacteria a place to hide. This facilitates the bacteria's ability to evade immune system detection, leading to latent TB infection (LTBI)[15,19] .The detection and treatment of latent TB infection (LTBI) is critical to reducing TB cases worldwide and ultimately eliminating the disease. Granulomas, tiny structures that aid in capturing the bacteria, are formed by the body early on. Because of VEGF, they are brimming with blood vessels and encircled by immune cell rings. The immune cells within, particularly the macrophages, begin to alter and organize into layers as the granuloma grows. Around a fibrous layer, which encircles a core composed of macrophages, lymphocytes create a ring on the exterior. Most of the time, people with these granulomas are healthy and do not infect others[20,21].Researchers have discovered that M. tuberculosis ingeniously converts specific immune cells, known as macrophages, into foam cells by using a fatty chemical called mycolic acid. A caseous granuloma, which is essentially a soft, cheese-like core packed with these foam cells and numerous dead immune cells, can form in the center of the granuloma as the infection worsens[22]. When tuberculosis progresses, the granuloma's soft center may degrade and create a hollow area. When that occurs, the disease can become active and spread more readily throughout the body because the germs that are imprisoned inside may be able to escape[23] .As a result, LTBI reactivation and the subsequent development of symptoms may allow the bacteria to spread to an Alternative host, thus sustaining A recent infection cycle. Additionally, Mtbc is disseminated via lymphatic endothelial cells and the bloodstream[24,25]. Extrapulmonary TB (EPTB) is a condition where TB spreads to other sections of the body and doesn't always stay in the lungs. Numerous organs, including the kidneys or reproductive organs, the lymph nodes, the lining around the lungs, the bones and joints, and potentially other organs, can develop this form of tuberculosis[26]. Future improvements in treatment may depend on our ability to comprehend how tuberculosis truly manifests in the body. Although Mycobacterium TB was discovered more than a century ago, it continues to cause a great deal of suffering, disease, and fatalities worldwide. Even more concerning is the increase in drug-resistant TB; the World Health Organization estimates that in 2021, there were around 450,000 newly identified cases of TB that did not react to rifampicin, one of the primary TB medications[27]. The spread of HIV has been closely associated with the increase in drug-resistant TB. Indeed, the vast majority of the early drug-resistant TB outbreaks were observed in individuals with both HIV and Mycobacterium tuberculosis (Mtb) infections[28,29].Furthermore, the detrimental impact of the COVID-19 pandemic has hindered attempts to detect and manage TB patients, erasing much of the progress made in recent years in the fight against the illness[30,31] .It is crucial to continue looking for better TB therapies because of this. Scientists have been investigating whether the BCG vaccine can help prevent the disease, but the findings thus far indicate that it is not very effective at producing long-term immunological protection[32–34] .Advancements in pathogen- host interaction studies and the evolutionary research of M. tuberculosis present valuable opportunities to identify Factors that influence pathogenicity and virulence, potentially leading to the rise of innovative tuberculosis Treatments[35].

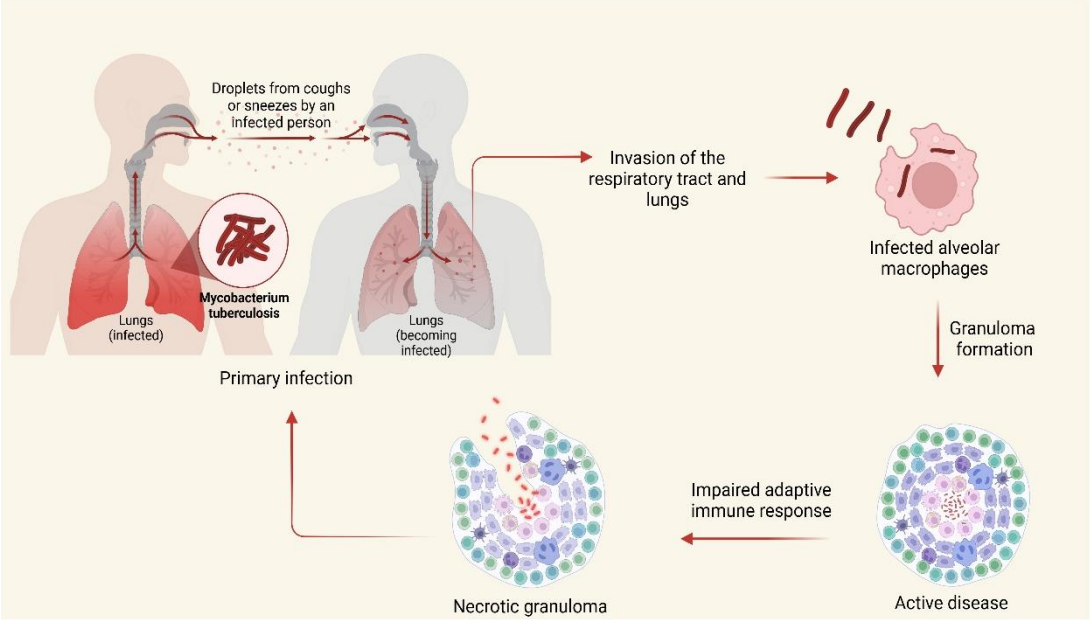

Figure 2:Pathophysiology of pulmonary TB.

Primary Anti-TB Drug Regimen

The four antibiotics that are currently used to treat drug-susceptible tuberculosis (DS-TB) are isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), as shown in Figure 3. These medications were all created about 60 years ago [36]. For this four-drug regimen to accomplish high cure and success rates, it must be administered for at least six months, usually in directly observed treatment (DOT). Two phases make up the therapy: the first involves taking all four antibiotics for the first two months, and the second involves using both isoniazid (INH) and rifampicin (RIF) for the final four months to eradicate any Inactive bacteria that may still be present[36].

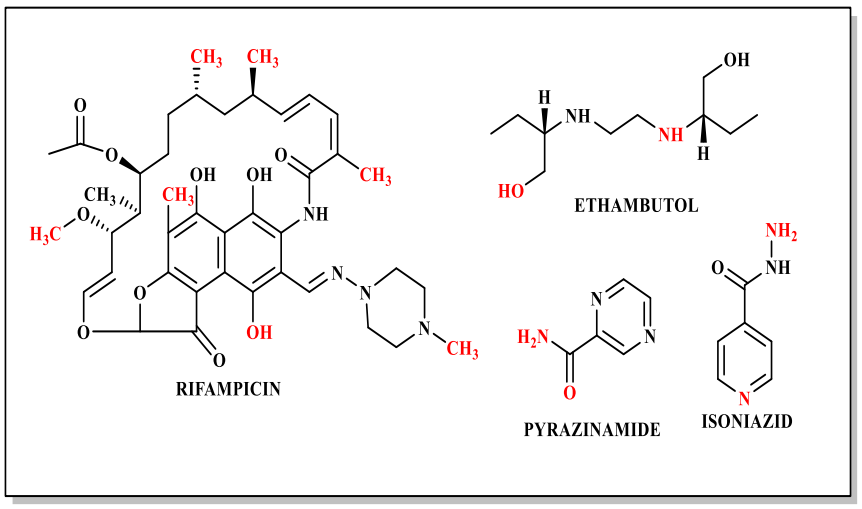

Figure 3: The four first-line anti-TB drugs

Multi-Drug Resistant Tuberculosis Crisis

Drug-resistant TB (DR-TB) can be difficult to cure, and the type of resistance the TB bacteria have often determines how well a patient reacts to treatment. When the infection no longer reacts to isoniazid and rifampicin, the two primary and most successful medications often used to treat TB, it can develop into multidrug-resistant TB (MDR-TB), one of the more severe types[27]. There were an expected 450,000 cases of multidrug-resistant TB (MDR-TB) in 2021. Although that is still a significant amount, it is far less than the number of cases of drug-susceptible, routine TB (DS-TB)[27]. The second-line treatment for MDR-TB, as advised by the WHO in 2019, as shown in Figure 4, lasts 18 to 20 months, depending on how

well the patient responds to treatment. A minimum of four drugs are usually administered to patients during the first phase of MDR-TB treatment: one from group B (e.g., terizidone/cycloserine or clofazimine) and three from group A (linezolid, bedaquiline, and either moxifloxacin or levofloxacin). The next stage of treatment should involve continuing at least three of the other medications after bedaquiline is stopped. To maintain the effectiveness of the treatment, two medications from group B should be introduced if only one or two group A medications are present[37]. In the event that the TB germs do not react to one or more of the primary therapy medications, physicians will add additional treatments from group C. This covers medications such as imipenem, meropenem, pyrazinamide, 4-aminosalicylic acid, ethambutol, delamanid, streptomycin or amikacin, ethionamide or prothionamide, and high-dose isoniazid. By doing so, the treatment is strengthened and the resistant TB strain is repelled[37,38]. Compared to the earlier, lengthier regimens, the WHO recommended in 2020 a shorter, all-oral treatment for those with MDR-TB that would last 9 to 11 months. This was done to make it simpler for patients to complete their medication[39]. This shortened course of therapy begins with a high dosage of isoniazid (INH), BDQ, clofazimine, ethionamide or prothionamide, moxifloxacin or levofloxacin, and clofazimine, PZA, and Ethambutol (EMB) is administered for the first four months of treatment. Table 2 describes the mechanism of action, target, drug resistance, and side effects of first- and second-line drugs. However, this period may be prolonged to six months if the patient's test findings, such as a sputum smear or culture, are still positive at that time. Bedaquiline (BDQ) should always be used for the entire six months. The second phase of treatment, which consists of EMB, pyrazinamide (PZA), clofazimine, and either moxifloxacin or levofloxacin, lasts for five months[39]. Notably, delamanid (DLM) and bedaquiline (BDQ) are the first novel TB medications with entirely different mechanisms of action to be licensed in more than 50 years. Recently, they were included in the list of second-line treatments. To put that into perspective, one of the most widely used TB medications, rifampicin (RIF), was approved in Italy in 1968 and in the United States in 1971[40,41].The first antibiotic of its sort, bedaquiline, was licensed by the US Food and Drug Administration (FDA) in late 2012. Additionally, the European Medicines Agency (EMA) approved it the next year, in 2013. approved the use of bedaquiline (BDQ) and delamanid (DLM) for people with multidrug-resistant tuberculosis (MDR-TB)[40] . When deciding which regimen will give each patient the best treatment outcome, many factors need to be considered. Individuals with MDR-TB who satisfy the following requirements for eligibility should be given the shortest all-oral BDQ-containing regimen (with at least shown RIF resistance): (1) fluoroquinolone resistance has been ruled out because fluoroquinolone susceptibility testing must be completed before the start of the shorter regimen; (2) no second-line treatment medication has been used for longer than a month (unless tests were conducted to confirm susceptibility to these medications); (3) no drug in the shorter regimen has been used with resistance or suspected inefficacy other than INH; (4) no severe extrapulmonary disease; and (5) no extensive tuberculosis.

A lengthier treatment plan can be required if a patient is not eligible for the shorter all-oral treatment or if doctors must begin treatment before test results establish which medications will be effective. This type of reassessment was required in seven out of twenty-three patients, indicating that it is a reasonably typical component of MDR-TB management.[39] .Drug-resistant TB that is more severe is called XDR-TB. Because MDR-TB is resistant to two important TB medications, isoniazid (INH) and rifampicin (RIF), it is already difficult to treat; however, XDR-TB is more severe. Additionally, it is resistant to injectable second-line medications such amikacin and, at a minimum, one fluoroquinolone, such as levofloxacin or moxifloxacin, making treatment even more challenging[42]. There aren't many remaining therapeutic options for XDR-TB because it is so drug-resistant. This has resulted in dangerously high fatality rates and makes it much more difficult to cure. It's a major worry because it increases the possibility that tuberculosis will become as fatal as it was before the invention of antibiotics[43].MDR-TB and the more severe XDR-TB are thought to be separated by pre-XDR-TB. It indicates that the TB is resistant to both an injectable second-line medication and a fluoroquinolone in addition to the standard MDR-TB medications. Both pre-XDR and XDR-TB treatment can be drawn out, typically taking 14 to 24 months. Starting with an intensive phase and ending with a continuation phase, the treatment is administered using a combination of second-line medications to which the TB germs are still susceptible[42]. The US FDA has approved the BPaL regimen, a new, shorter treatment for XDR-TB that consists of linezolid, pretomanid (PMD), and bedaquiline (BDQ). However, this medication should only be administered in research settings and to patients who have never had BDQ or linezolid before[38].The most recent addition to the list of TB treatment alternatives is pretomanid (PMD), which is comparable to delamanid (DLM). Only persons with XDR-TB or MDR-TB who do not react to treatment or develop drug intolerance are eligible for it; the US FDA approved it in 2019 as part of the BPaL regimen[44]. There are two primary ways that MDR-TB or XDR-TB can spread: (1) an individual can contract it directly from another sick person, or (2) resistance may arise if TB drugs are misused or patients are not adequately treated[38,39]. The average course of therapy for MDR-TB and XDR-TB is significantly longer than that for ordinary TB, often taking up to two years. Additionally, the medications used to treat these drug-resistant strains are frequently more costly, rougher on the body, and less effective than the standard TB medications[45].These challenges make it extremely difficult for patients to adhere to their treatment plans, which makes it easier for the illness to spread throughout communities and keeps tuberculosis a severe and ongoing worldwide issue.

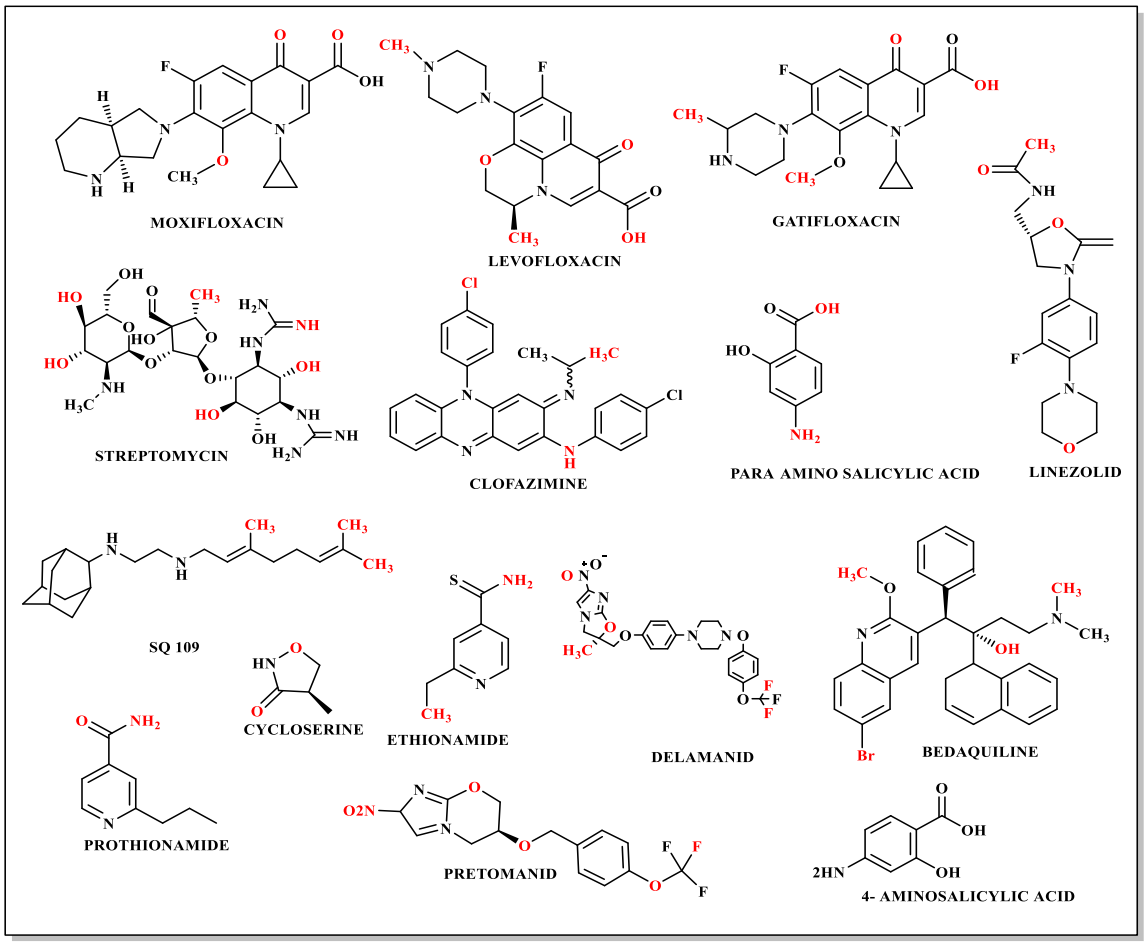

Figure 4: Current second-line anti-TB drug

Table 2: Overview of First and Second-Line Anti-TB Drugs: Mechanism, Targets, Resistance, and Side Effects *[1,46]* .

Drug	Activity	MOA	Target	Resistant gene	Side effect
Rifampicin	Bactericidal	Inhibits bacterial RNA synthesis	RNA polymerase β-subunit	rpoB	Rashes, nausea, dyspepsia, hepatotoxicity, and abdominal discomfort
Isoniazid	Bactericidal	Inhibition of the metabolism of NAD, lipids, carbohydrates, and cell wall mycolic acid	InhA(enoyl-ACP reductase)	katG, AhpC, and inhA	CYP450 interactions, peripheral neuropathy, and hepatotoxicity
Ethambutol	Bactericidal	inhibition of the production of arabinogalactan in the cell wall	arabinosyltransferase,	embB	Optic neuropathy
Pyrazinamide	Bactericidal	Pyrazinamide disrupts membrane	Cell membrane and energy metabolism	pncA	GI disturbance, hepatotoxicity, gout

		transport and depletes energy			
Streptomycin	Bacteriostatic	inhibits ribosomal protein synthesis	30S ribosomal subunit (16S rRNA and S12 ribosomal protein)	RpsL,rrs gidB	Nephrotoxicity, ototoxicity
Ethionamide	Bacteriostatic	inhibits mycolic acid biosynthesis	NADH-dependent enoyl-ACP reductase (*InhA*)	*ethA, ethR, inhA.*	peripheral neuropathy, hepatotoxicity, hypothyroidism, dysglycaemia
Fluoroquinolone	Bactericidal	inhibits bacterial DNA replication and transcription	DNA gyrase (topoisomerase II)	*gyrA*, *gyrB*, and *pstB*.	QT prolongation, tendonitis, hypoglycemia, psychiatric disturbance
Para-amino salicylic acid (PAS)	Bacteriostatic	inhibits folate synthesis by interfering with dihydrofolate metabolism.	Dihydrofolate synthase (*FolC*) and dihydrofolate reductase (*DfrA*)	*folC, dfrA.*	Hepatotoxicity, dysglycaemia, hypothyroidism
Cycloserine	Bacteriostatic	inhibits peptidoglycan synthesis	*D-alanine racemase* (*Alr*) and *D-alanine:D-alanine ligase* (*Ddl*)	*alrA*	Psychiatric disturbance, peripheral neuropathy
Kanamycin & Amikacin	Bactericidal	Inhibit protein synthesis	16S rRNA of the 30S ribosomal subunit.	*rrs (16S rRNA), (aac).*	Nephrotoxicity, ototoxicity
Capreomycin & Viomycin	bacteriostatic	Inhibit protein synthesis	23S rRNA (50S ribosomal subunit).	*rrs (23S rRNA), tylA*	Nephrotoxicity, ototoxicity
Linezolid	bacteriostatic	inhibits protein synthesis	50S ribosomal subunit (23S rRNA).	*rrl*	Dysglycemia, peripheral neuropathy, ocular neuropathy, and myelosuppression
Clofazimine	bactericidal,	disrupts the Mycobacterial membrane	Mycobacterial membrane.	*Rv0678*	QT prolongation, hepatotoxicity, gastrointestinal disorders, and neurological disorders, altered skin pigmentation
Bedaquiline	bactericidal	Inhibits ATP synthase, disrupting bacterial energy production.	ATP synthase (subunit C, *AtpE*)	*AtpE (mutations A63P, 166M)*	QT prolongation, CYP450 interactions
Delamanid	bactericidal,	inhibits mycolic acid synthesis after activation by F420-dependent nitroreductase,	Mycolic acid biosynthesis	*ddn, fgd1*	QT prolongation, CYP450 interactions

		disrupting the bacterial cell wall.			
SQ-109	bactericidal	inhibits mycobacterial cell wall synthesis	*MmpL3* transporter	*MmpL3*	Gastrointestinal Issues, Hepatotoxicity QT interval prolongation

Novel therapeutic advancement on TB

Currently, six more medications are in the discovery or preclinical stages of development, while seventeen more medications are undergoing phase I or II clinical trials, as shown in Figure 5. Eleven of the medications in clinical studies now represent completely novel chemical classes. Among the others are the diarylquinolines TBAJ-587 and TBAJ-876, which are related to bedaquiline (BDQ), and the oxazolidinones delpazolid, sutezolid, and TBI-223, which are comparable to cycloserine and linezolid (LZD). Pretomanid (Pa) was approved in 2019, and as of the time of writing, only one new medication—sudapyridine—has advanced to phase III studies or obtained regulatory approval. A medication from a new class called telacebec, which targets the mycobacterial cytochrome bc1 complex—which is necessary for the synthesis of ATP—is one especially intriguing option. Telacebec has been shown in a proof-of-concept trial to increase sputum clearance rates while preserving a side effect profile comparable to that of existing licensed medications.Telacebec is anticipated to become the third recently licensed contemporary medication class with action against tuberculosis if current clinical trials continue to produce comparable outcomes[47]. This would be a significant step forward, especially because many of the current existing medications have severe side effects or may not function as effectively development are classified similarly to existing drugs, and as such their use in additive or substitutive places for their relative counterparts will be precluded due to concerns regarding toxicity or resistance. Additionally, it's important to note that the majority of these medications are in the development stage as oral formulations, which suit patient preferences and could result in increased treatment compliance and cure rates.

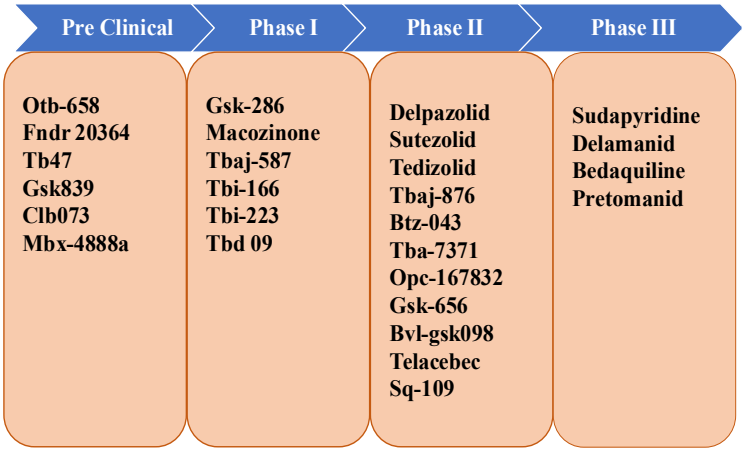

Figure 5: Emerging anti-tuberculosis drugs are currently under development [67].

Recent Perspectives on TB Vaccines

There is an urgent need for more economical and effective TB vaccines because of the high rates of TB-related sickness and mortality as well as the expanding global problem of drug-resistant TB. The creation of affordable and extremely effective TB vaccinations continues to be a top goal, even as advancements are being made in the creation of novel antibiotic therapies. However, despite the disease's enormous worldwide impact, this effort is hampered by the lack of funds available for clinical trials[39].(World Health Organization 2022). The development of TB vaccines has historically concentrated on inducing a CD4+ Th1 T-cell response to evaluate the immunological potential of vaccine candidates. The precise processes that offer complete protection against tuberculosis, however, are yet unclear. It has been suggested that depending only on these cells' production of IFN-γ may not be sufficient and does not guarantee that a vaccine would work well in actual clinical settings[48].Although the significance of CD8+ T cells in tuberculosis immunity has been highlighted, they have not been adequately prioritized as target cells in the design of TB vaccine candidates[49,50] .The development of TB vaccines is aided

by the joint research and innovation effort known as the Tuberculosis Vaccine Initiative (TBVI). In collaboration with the Global TB Vaccine Partnership (GTBVP), it conducts its operations. According to information obtained on September 2, 2024, from TBVI (https://www.tbvi.eu/what-we-do/pipeline-vaccines/), the current TB vaccine pipeline includes 19 candidate vaccines in different stages of clinical development belonging to other categories, as shown in Figure 6. Live attenuated mycobacterial These include vaccinations derived from dead or broken-down TB bacteria used to help treat the disease; protein-based vaccines supplemented with unique chemicals to increase their efficiency; and others that employ harmless viruses to deliver bits of the TB bacterium and teach the immune system to resist it. Increasing investment to support production costs and improving the effectiveness of preventive anti-Mtb vaccines are considered crucial measures to ensure that vaccines are available to people who need them most. Supported by encouraging developments in preclinical and clinical studies, there is increasing hope for the ongoing TB vaccine research[51]. New approaches to vaccine design have been made possible by recent developments in materials science, which enable more accurate delivery, greater adjuvant performance, better dose-sparing effects, increased stability, and controlled release at the administration site[52]. Nanoparticles have been utilized to enhance the immune response in addition to delivering antigens. Recently, yellow carnauba wax nanoparticles coated with a fusion protein consisting of three essential Mtb antigens—Acr, Ag85B, and HBHA—were used to create Nano-FP1, a promising novel TB vaccine. It has so far produced positive preclinical test findings[53]. mRNA technology has advanced significantly, particularly after the COVID-19 pandemic brought significant advancements. The timing is right to use these advancements to create a novel, potent TB vaccine. The concept of use mRNA to treat TB is not wholly novel; in 2004, scientists in the UK demonstrated that an mRNA-based vaccination offered mice a slight but significant defense against Mtb[54]. In a recent attempt to develop an mRNA vaccine for tuberculosis, researchers looked at nine distinct proteins to determine which ones would best elicit an immunological response. To create a vaccination that could trigger the body's cellular and antibody-based defenses, they employed sophisticated immunoinformatics technologies. 30 specific epitopes, a TLR4 agonist adjuvant known as RpfE, elements to aid in intracellular delivery, a secretion enhancer, and specialized linkers were all incorporated into the vaccine blueprint. According to early estimates, this vaccine may be able to protect 99.38% of the world's population, and preliminary research indicated that it is both safe and efficacious. The researchers used a computer-based immunological simulation of the vaccination to support their hypothesis. They examined its ability to bind to TLR-4 and TLR-3, two important immunological receptors, and predicted its three-dimensional structure. The stability of these linkages was established by additional simulations. Given these positive outcomes, the team feels their vaccine is a serious candidate to combat tuberculosis and is prepared to proceed with laboratory testing to determine its effectiveness in real-world settings[55].In a recent study, researchers created ID91, a potential next-generation TB vaccine. They developed two versions of it: a cutting-edge replicating RNA (repRNA) version that was administered via a specially made nanostructured lipid carrier and a fusion protein that was paired with a synthetic TLR4-activating adjuvant (a glucopyranosyl lipid in a stable emulsion). Protein subunit and RNA-based vaccines engage the immune system in distinct ways, targeting various regions of the ID91 protein. In early testing using only one preventative dosage, both kinds demonstrated that they could lower the number of tuberculosis germs in the lungs compared to no therapy. What's particularly intriguing is that the best outcomes came from utilizing a mix of both—beginning with the RNA vaccination and then boosting with the protein vaccine, or combination vaccinations produced a distinct mixture of antibody and T-cell immune responses and caused the largest decrease in bacterial levels. For the first time, scientists have demonstrated that repRNA technology may be a viable option for creating TB vaccines. To maximize this strategy going forward, they advise concentrating on Mtb antigens with a high priority that contain both CD4+ and CD8+ T-cell targets[56]. The development of an mRNA-based vaccination to prevent tuberculosis is now feasible, but it still depends in determining the optimum antigen targets, which has proven to be a challenging effort thus far. However, there is increasing hope, particularly in light of the World Health Organization's establishment of new mRNA technology transfer hubs. These hubs are thought to be revolutionary since they provide low- and middle-income nations with the means to manufacture their own medications, vaccinations, and diagnostic tests. Many experts think that since mRNA technology has advanced so much, particularly during the COVID-19 epidemic, there has never been a better moment to use it to develop a potent TB vaccine.

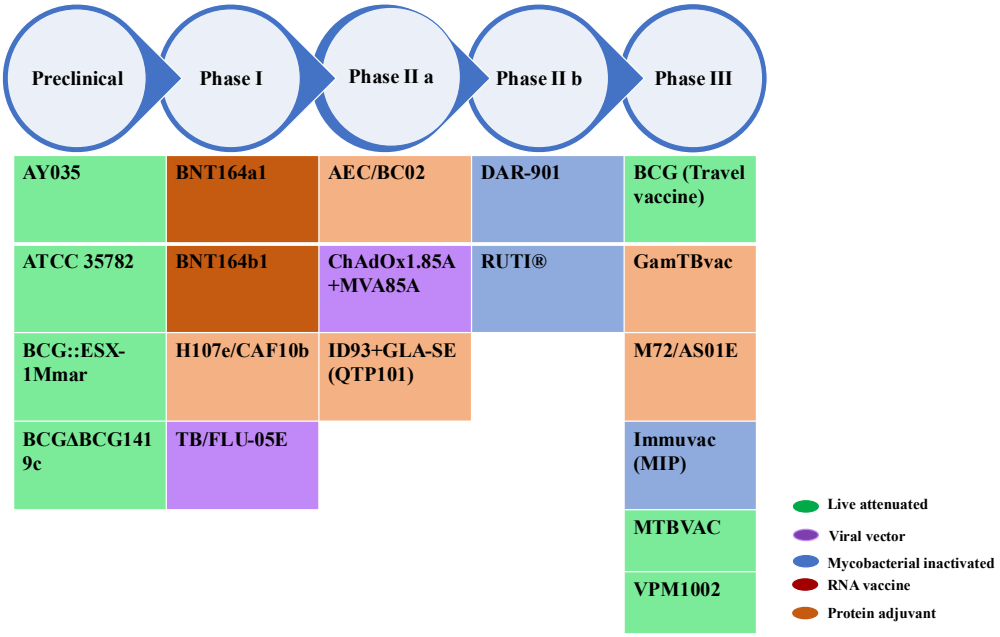

Figure 6:Summary of TB Vaccine Candidates in Ongoing Clinical Trials (last update 2 September 2024.

Artificial Intelligence (AI) Automating illness diagnosis through machine learning is one of the primary applications of AI in tuberculosis. Establishing expert systems through a machine learning approach based on TB patients' clinical, radiographic, and laboratory data is a popular tactic. It's interesting to note that machine learning has been shown to help doctors identify drug-resistant TB or diagnose pulmonary TB[57–64].for example, Lopes et al. offered three suggestions for using pre-trained convolutional neural networks as picture feature extractors to identify tuberculosis[57].Jaeger et al.reported that Researchers are experimenting with machine learning and visual analysis to automatically distinguish between drug-resistant and drug-sensitive tuberculosis in chest X-rays. The method employs an artificial neural network in conjunction with a set of shape and texture-based features to distinguish the two[59].Using independent laboratory data, we also successfully created a GBM model based on the machine learning approach, which could be very helpful as a tool for identifying active TB[65]. Furthermore, risk assessment for Illness and death is another area of AI-driven interventions in a health environment. To help TB programs run more efficiently, Hussain et al. developed a Procedure that uses three methods based on machine learning to calculate the probability of TB treatment failure[66].

3. CONCLUSION

Tuberculosis continues to be an important worldwide health issue, with millions of new cases reported annually and an increasing presence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Despite decades of advancements in diagnosis, treatment, and vaccination, the disease continues to cause substantial illness and death on a global scale. The disruptions caused by the COVID-19 pandemic exacerbated TB control problems by increasing transmission rates, interrupting treatment, and delaying diagnosis. To mitigate these setbacks, new efforts are needed to foster innovation, improve accessibility, and strengthen international collaboration. Despite being widely used, the Bacillus Calmette-Guérin (BCG) vaccine has a poor propensity to prevent adult pulmonary tuberculosis, which emphasizes the urgent need for more potent vaccinations**.** Clinical trials are currently being conducted on several promising options, including protein subunit vaccines, viral vector-based formulations, and mRNA-based platforms, aimed at producing more robust and long-lasting immune responses. Additionally, the potential for broader and more effective protection has increased due to innovations in novel adjuvants and vaccine delivery systems utilizing nanoparticles. However, to ensure equitable vaccination distribution, particularly in high-burden areas, major challenges such as budgetary constraints, regulatory hurdles, and large-scale production issues must be addressed. Drug-resistant TB is becoming increasingly prevalent, highlighting the inadequacy of current antibiotic therapies. Although newer drugs like bedaquiline, pretomanid, and delamanid have shown improved treatment outcomes, significant challenges remain due to their high costs and limited availability moreover, prolonged treatment regimens and associated side effects often lead to poor adherence, further exacerbating drug resistance. As a result, alternative therapeutic approaches, including host-directed therapies and immunomodulators, are being explored to improve treatment efficacy and patient outcomes.

Digital health and artificial intelligence (AI) developments have brought about exciting new developments in tuberculosis (TB) treatment, especially in the areas of diagnosis and treatment monitoring. AI-driven models have shown promise in improving early detection and treatment strategy optimization. Examples of these models include machine learning

algorithms for chest X-ray interpretation and predictive tools for drug resistance. AI applications can also enhance resource allocation, ease patient monitoring, and support international TB surveillance initiatives. However, resolving issues with data security, healthcare infrastructure, and ethical considerations is necessary for the successful integration of AI into TB control programs. Even though TB research and control measures have made significant strides, the World Health Organization's (WHO) End-TB strategy is still very difficult to achieve. A comprehensive strategy is required to eradicate tuberculosis by 2035, which includes bolstering healthcare systems, increasing financing for research and development, and forging closer international alliances. Reducing TB incidence and fatality rates requires universal access to precise diagnostics, efficient therapies, and enhanced vaccinations, especially in environments with limited resources. Future TB control efforts should implement evidence-based strategies and capitalize on scientific and technological advancements to accelerate success. Combining state-of-the-art methods for diagnosis and treatment with enhanced TB surveillance systems and strengthened public health infrastructure will be necessary to overcome present challenges. A coordinated global effort involving social measures, well-organized prevention programs, and increasing financial commitment will be necessary to combat tuberculosis. Only through persistent and coordinated efforts will the international community be able to eradicate tuberculosis as a public health issue.

Conflict of Interest

The author has no conflict of interest.

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