

Drug Utilization Evaluation Among Tuberculosis Patient in District TB Center Mehsana

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Abstract: "Across the globe, tuberculosis (TB) is still a severe public health challenge. This is especially true in developing nations that are experiencing an upward trend in both the number of infections and resistance to treatments." The present study aimed to evaluate drug utilization patterns among tuberculosis patients attending the District TB Center, Mehsana. A retrospective observational analysis was conducted to assess prescribing trends, rationality of therapy, adherence to national treatment guidelines, and the prevalence of drug-resistant cases. Data were collected from patient treatment records, including demographic characteristics, diagnostic methods, type of TB (pulmonary or extrapulmonary), and prescribed anti-tubercular regimens. The research mainly examined the commonly used first-line anti-tuberculosis medications, including isoniazid, rifampicin, pyrazinamide, and ethambutol. In addition, it also considered second-line drugs that are prescribed in cases of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, where standard treatments are no longer effective. The study also explored the use of newer treatment approaches, particularly the BPaLM regimen, which combines bedaquiline, pretomanid, linezolid, and moxifloxacin. This modern combination has been developed to improve outcomes in drug-resistant tuberculosis and offers a more advanced option compared to traditional therapies. Findings indicated that most patients received standardized weight-based dosing in accordance with national TB control guidelines. The use of molecular diagnostic tools such as GeneXpert improved early detection of rifampicin resistance, facilitating appropriate regimen selection. Overall, drug prescribing patterns were largely rational and guideline-compliant. However, continuous monitoring is essential to prevent resistance development, ensure patient adherence, and optimize therapeutic outcomes. Drug utilization evaluation serves as an important tool for assessing treatment effectiveness, safety, and quality of care in tuberculosis management.

Keywords:

- Tuberculosis
- Drug Utilization Evaluation
- Anti-tubercular Therapy
- Multidrug-Resistant Tuberculosis (MDR-TB)
- BPaLM Regimen Rational Drug Use
- GeneXpert
- Pharmacovigilance

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I. INTRODUCTION

Tuberculosis (TB) is caused by a bacterium (or germ) called *Mycobacterium tuberculosis*. majority Tuberculosis (TB) in humans is mainly caused by *Mycobacterium tuberculosis*. However, other related bacteria, such as *Mycobacterium bovis*, can also lead to TB infection. The disease most commonly targets the lungs, but it is not limited to them. TB can spread to other organs like the brain, kidneys,

or spine. In some cases, it may involve more than one area of the body at the same time—for instance, both the lungs and the lymph nodes can be affected together.[1]

Tuberculosis spreads through the air when a person with active TB releases bacteria by coughing, sneezing, or even spitting. Despite how easily it can spread, TB is both preventable and treatable with proper care. It is estimated that nearly one-fourth of the world's population carries the TB

bacteria. However, only a small proportion—around 5 to 10 percent—of those infected will go on to develop symptoms and active TB disease during their lifetime.[2]

the larynx, lymph nodes, pleura, brain, kidneys, bones, or joints. In fact, TB has the potential to develop in almost any organ of the body. [5]

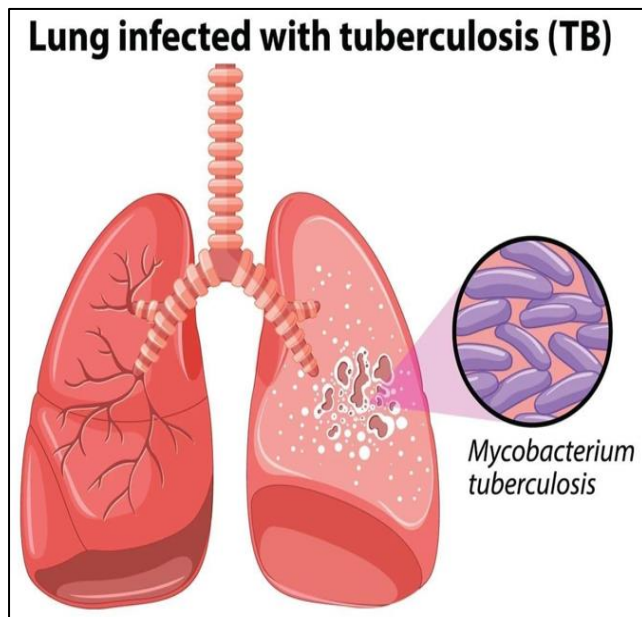


Fig 1 Lung Infected with Tuberculosis

II. HISTORY

Tuberculosis was mentioned in the ancient Indian medical scripture Sushruta Samhita, which dates back to around 606 BCE, showing that the disease has been recognized and studied since early historical times.[3] In 1906, India set up its first tuberculosis sanatorium at Tiluania near Ajmer in Rajasthan, marking an important step in organized TB care. This was followed by the establishment of the country's first TB dispensary in 1917. With the advancement of medical technology, X-ray diagnosis became available by 1925, making detection of the disease more accurate. After independence, the Government of India introduced several regional and national initiatives to control and reduce TB cases. With support from WHO and UNICEF, a BCG vaccine production center was established in Guindy, Madras. This led to the launch of a nationwide BCG vaccination campaign in 1951 to help prevent the spread of tuberculosis.[4]

➤ Types of Tuberculosis:-

- **Pulmonary TB:**

Pulmonary tuberculosis is the most frequently seen type of TB and mainly involves the lungs. Individuals with this form often experience a persistent cough and may show abnormal findings on a chest X-ray. Because the lungs are affected, these patients can spread the infection to others through the air. The majority of TB cases fall under this category. [5]

- **Extrapulmonary TB:**

Extrapulmonary tuberculosis occurs when the infection affects areas other than the lungs. It can involve parts such as

- **Transmission and Pathogenesis:**

Mycobacteria are a family of bacteria responsible for several diseases. Certain species are grouped under the *Mycobacterium tuberculosis* complex because they cause tuberculosis or TB-like illnesses. *M. tuberculosis*, often referred to as tubercle bacilli, is the primary organism responsible for TB. Other related species that can infect humans include *M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*. Overall, tuberculosis in humans is mainly caused by *Mycobacterium tuberculosis*. [6]

TB infection starts when a person inhales airborne *M. tuberculosis* bacteria. These bacteria travel deep into the lungs and settle in tiny air sacs called alveoli. There, they encounter alveolar macrophages, which are immune cells designed to destroy invading organisms. Although macrophages attempt to eliminate the bacteria, *M. tuberculosis* has the ability to survive inside these cells, leading to a long-lasting infection. [7]

The defense response begins when the macrophage recognizes the invading bacterium through receptors on its surface. It then surrounds and engulfs the bacterium in a process known as phagocytosis. [8]

After engulfment, the bacterium becomes enclosed within a structure called a phagosome. This phagosome later fuses with a lysosome—an organelle filled with digestive enzymes—forming a phagolysosome. [9]

Within the phagolysosome, enzymes are released in an attempt to break down and destroy the invading microorganism. [10]

Granulomas, which are clusters of immune cells formed to contain the infection, are most commonly found in the lungs but may develop in other parts of the body as well. Contained within granulomas, there are no outward symptoms and the infection is latent.[11] However, if the immune system is unable to control the infection, the disease can progress to active TB, which can cause significant damage to the lungs and other organs.[12]

If tuberculosis bacteria enter the bloodstream from a damaged area of tissue, they can travel to different parts of the body. This spread allows the infection to establish multiple sites, or small pockets of disease, in various organs.[13]

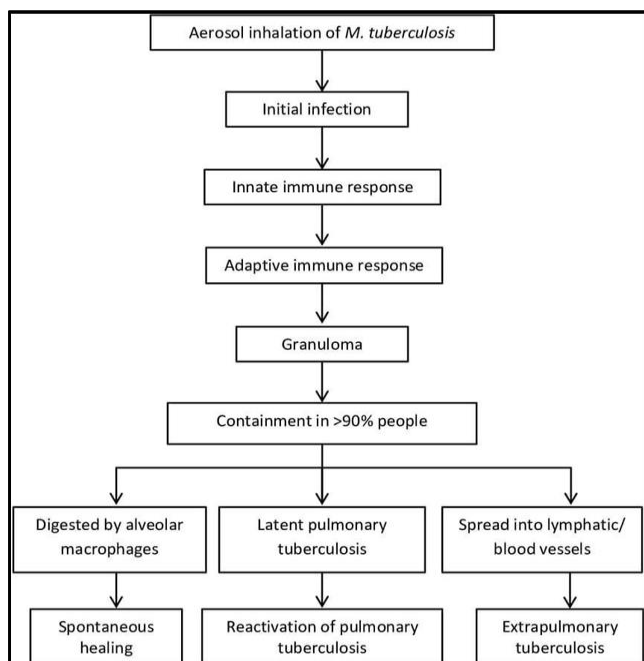


Fig 2 Transmission of Mycobacterium Tuberculosis Bacteria

➤ *Signs and Symptoms:-*

- Fever
- Chills
- Night sweats
- Weight loss
- Not wanting to eat
- Tiredness
- Not feeling well in general
- Pain near the site of infection [14]

✓ *Note:*

The signs and symptoms of extrapulmonary tuberculosis vary based on the specific organ or area of the body that is affected. Since the infection can involve different systems, the clinical features depend on where the disease is located.[14]

➤ *Diagnosis of Tuberculosis:-*

- **Chest Imaging:** Chest X-ray is essential to detect pulmonary abnormalities consistent with active TB.[15]
- **Sputum Smear Microscopy (Acid-Fast Bacilli, AFB Stain):** Rapid, inexpensive; identifies acid-fast bacilli under a microscope. Sensitivity is limited (~50%).[16]
- **Nucleic Acid Amplification Tests (NAATs)** – such as the Xpert MTB/RIF (GeneXpert) assay – are advanced molecular tests used to detect tuberculosis. These tests identify the DNA of Mycobacterium tuberculosis and can also determine resistance to rifampicin within about two hours. Compared to traditional culture methods, NAATs are much faster and offer high sensitivity and specificity, making them very reliable for early diagnosis.[17]
- **Culture test (Liquid and Solid Mycobacterial Culture):** The gold standard for confirming active TB; allows for growth and identification of M. tuberculosis, albeit slow (weeks).[18]

III. TUBERCULIN SKIN TEST (TST)

In this test, a small amount of tuberculin is injected just beneath the skin, usually on the inner side of the forearm. After 48 to 72 hours, a healthcare professional examines the injection site to check for any swelling or raised area. The size of this reaction is measured to decide whether the test result is positive or negative for tuberculosis infection.[19]

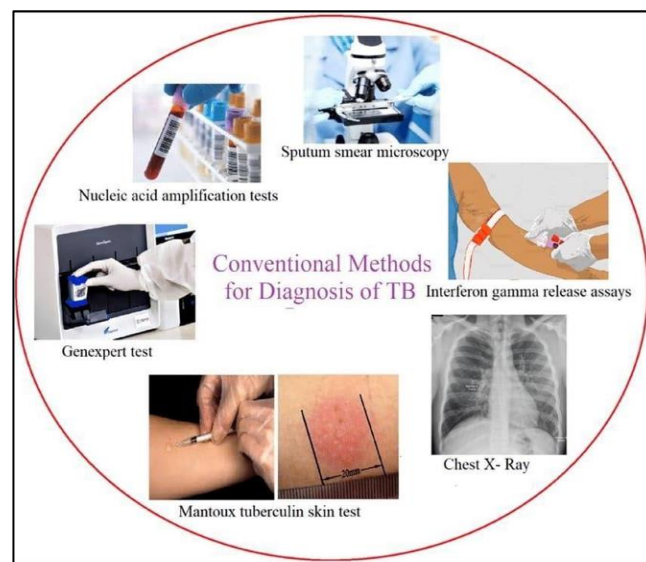


Fig 3 Conventional Methods for Diagnosis of TB

The diagnosis of tuberculosis involves a combination of traditional and modern techniques to ensure accurate and early detection. Conventional methods include sputum smear microscopy, chest X-rays, and the Mantoux (tuberculin skin) test. In addition, advanced molecular tests such as GeneXpert and other nucleic acid amplification tests are used to rapidly identify the bacteria and detect drug resistance. Interferon-gamma release assays (IGRAs) also play a role in confirming TB infection, helping clinicians make timely and reliable decisions.

➤ *Evaluation of Tuberculosis Treatment:-*

- **Sanatorium era:** In Ancient times, People once believed that rest and fresh air had natural healing benefits.. In 19th century, sanatorium treatment was preferred to the patient where they can rest and healthy diet was prescribed. They give some herbal drugs but not given any specific treatment drugs.[20]
- A major turning point occurred in the 1940s when streptomycin was discovered by Selman Waksman. It became the first antibiotic proven to be effective against tuberculosis, opening a new chapter in the treatment and control of the disease.[20]
- 4-Aminosalicylic acid is also called para-amino salicylic acid. It was initially synthesized in 1902, but it was not introduced for medical treatment until 1943. [21]
- As a structural analogue of para-aminobenzoic acid (PABA), this drug interferes with folate metabolism by competitively interacting with enzymes involved in the pathway, which ultimately restricts the growth of tubercle

bacilli. Although it has shown strong anti-tubercular activity in laboratory studies as well as in clinical use, its role in treatment must be considered alongside other therapeutic factors.[22]

- Isoniazid first synthesized in 1912.[23]
- In 1952, isoniazid (INH, H) was introduced and quickly gained recognition as a breakthrough medication in the treatment of tuberculosis. Its success was largely due to its strong activity against *Mycobacterium tuberculosis*, demonstrated by its very low minimum inhibitory concentration (MIC), along with relatively low toxicity. At that time, a standard daily dose of 200 mg was prescribed, which was significantly higher—about ten times—than the minimum amount needed to produce an effective response..[24]
- Isoniazid has been a significant drug in TB treatment regimens since 1952. INH is a prodrug activated by the catalase-peroxidase KatG, creating a variety of radicals and adducts that inhibit the mycobacterium's production of the mycolic acids that make up its cell wall. This activity lends INH the ability to be a potent bactericidal agent. The drug also appears synergistic with other species produced by KatG and other medications used to treat TB. [25] However, mutations in the *katG*, *inhA*, *kasA*, and *ahpC* genes may cause resistance to INH therapy. *M. tuberculosis* resistance develops more rapidly with INH monotherapy.[26][27]
- Pyrazinamide was developed in 1936, but it was only many years later, around 1972, that it became commonly used as part of standard tuberculosis treatment.[28]
- Pyrazinamide enters actively growing *Mycobacterium tuberculosis* cells, where it is acted upon by a specific bacterial enzyme. This enzyme converts pyrazinamide into its active form, known as pyrazinoic acid, which is responsible for its anti-tubercular effect.. Pyrazinoic acid can leak out under acidic conditions to be converted to the protonated conjugate acid, which is readily diffused back into the bacilli and accumulates intracellularly. The net effect is that more pyrazinoic acid accumulates inside the bacillus at acid pH than at neutral pH. Pyrazinoic acid was thought to inhibit the enzyme fatty acid synthase (FAS) I, which is required by the bacterium to synthesize fatty acids. However, this theory was thought to have been discounted.[29]
- Ethambutol was introduced in 1961 and is still recognized by the World Health Organization as an essential medicine for TB treatment.. Ethambutol is bacteriostatic against active against drug susceptible replicating mycobacterium bacilli. Its mechanism of action is to disrupt arabinogalactan synthesis by inhibiting the enzyme Arabinosyl transferase. Disruption of the arabinogalactan synthesis inhibits the formation of mycolyl-arabinogalactan-peptidoglycan (mAGP) complex and thus leads to increased permeability of the cell wall. Ethambutol resistance is primarily associated with missense mutations in the *embB* gene. However, mutations in *embB* codon 306 have been observed in clinical isolates susceptible to ethambutol. To clarify the role of *embB*, Starks et al. sequenced the ethambutol resistance-determining region in spontaneous ethambutol-

resistant mutants.[30]

- Rifampicin was identified in 1965, later introduced to the market in Italy in 1968, and subsequently received approval for use in the United States in 1971. [31][32]
- This antibiotic is naturally produced by the soil-dwelling bacterium *Ammycolatopsis rifamycinica*. [33]
- Rifampin works by killing bacteria through the inhibition of DNA-dependent RNA polymerase (RNAP), an enzyme essential for RNA synthesis. It blocks the progression of newly forming RNA strands or decreases the enzyme's ability to bind with short RNA fragments, thereby stopping RNA production. Importantly, rifampin selectively targets bacterial RNAP without significantly affecting the mammalian version of the enzyme, which helps limit side effects in humans. It is effective against both intracellular and extracellular *Mycobacterium tuberculosis*. [34][35][36]

➤ First-Line Drugs:

The standard first-line medications used to treat tuberculosis include isoniazid, a rifamycin group drug (most commonly rifampin, and less often rifapentine or rifabutin), pyrazinamide, and ethambutol. In certain treatment regimens, moxifloxacin may also be included alongside isoniazid, rifapentine, and pyrazinamide as part of first-line therapy. [37]

Revised National TB Control Programme District TB Centre, Mehsana			
Daily Dose Schedule for Adults (as per weight bands)			
Weight Band	Number of tablets		
	Intensive phase (4 FDC)	Continuation phase (3 FDC)	
	HRZE (2Month) 75/150/400/275 mg	HRE (4 Month) 75/150/275 mg	
25-34 kg	2	2	
35-49 kg	3	3	
50-64 kg	4	4	
65-75 kg	5	5	

Fig 4 Daily Dose Schedule for Adults (Weight Based)

Daily Dose Schedule for Paediatric TB (as per weight)				
Weight Band	Number of tablets (dispersible FDCs)			
	Intensive phase (2 Month)		Continuation (4 Month)	
	HRZ 50/75/150 mg	E	HR	E
4-7 kg	1	2	1	1
8-11 kg	2	2	2	3
12-15 kg	3	4	3	3
16-24 kg	2 + 1A*	3	4	4
25-39 kg	2 + 2A*	4	2 + 1A*	4

*A= Adult FDC (HRZE = 50/75/150 mg ; HRE = 50/75 mg / 100 mg)

Fig 5 Daily Dose Schedule for Paediatric TB (Wight-Based)

➤ Second Line Drugs:-

Second-line anti-tuberculosis drugs are used when standard first-line medicines are no longer effective, particularly in cases of multidrug-resistant TB (MDR-TB). Their main purpose is to treat strains of *Mycobacterium tuberculosis* that have developed resistance to routine therapy. Because these medicines are often the last effective option, it is essential to use them carefully and appropriately to maintain their effectiveness. In short, they provide an important backup when conventional treatment fails, highlighting the need for responsible and well-planned use.[38]

Drug class	Name of drug
Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)
Other core second-line agents	Ethionamide/Prothionamide Cycloserine/Terizidone Linezolid

Table 6 (“Classification of Second-Line Drugs Used in Tuberculosis Treatment”)

➤ Fluoroquinolones:-

Fluoroquinolones are bactericidal agents that inhibit DNA synthesis in bacteria. Early fluoroquinolones (e.g., ciprofloxacin) primarily target gram-negative bacteria, including *Pseudomonas* species. Newer agents (e.g., levofloxacin and moxifloxacin) have expanded coverage against gram-positive bacteria (e.g., *Staphylococcus* and *Streptococcus* species), *Mycobacterium* species and some anaerobes, but have reduced activity against *Pseudomonas* species.[39]

➤ Second-Line Injectable Agents: -

Amikacin (AM) and Kanamycin (KN) are two aminoglycoside antibiotics that serve as key second-line injectable drugs in the management of MDR-TB and XDR-TB. They act by interfering with bacterial protein synthesis, specifically by attaching to the 16S rRNA component of the 30S ribosomal subunit. [145]

Resistance to these aminoglycosides is commonly associated with mutations in the *rrs* gene, particularly at positions 1401, 1402, and 1484, as well as changes in the *eis* promoter region. [41][40] In addition to genetic mutations, other resistance mechanisms may involve enzymatic modification of the drug by aminoglycoside-modifying enzymes and decreased drug uptake by the bacterial cell.[40]

➤ MDR-TB (Multidrug-Resistant Tuberculosis):

The term drug-resistant TB commonly includes multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB). MDR-TB specifically refers to tuberculosis caused by strains of the *Mycobacterium tuberculosis* complex

that no longer respond to at least two of the most powerful first-line drugs—rifampicin and isoniazid. This resistance makes the disease more difficult to treat and requires alternative treatment regimens..[41]

Table 1 (“List of Medicines with Their Strength and Quantity for MDR-TB Management”)

Drug	Strength	Quantity
Levofloxacin	500 mg	30 tab
Levofloxacin	250 mg	30 tab
Linezolid	600 mg	30 tab
Clofazimine	100 mg	30 tab
Pyridoxine	50 mg	60 tab
Cycloserine	250 mg	90 tab

➤ XDR-TB: -

Extensively Drug-Resistant Tuberculosis :XDR-TB is a severe type of tuberculosis caused by strains of bacteria that are resistant to several of the most powerful anti-TB medications. It usually develops when multidrug-resistant TB (MDR-TB) is not treated properly or is poorly managed, allowing the bacteria to become even more resistant. Globally, it is estimated that nearly one-fourth of the population carries TB bacteria. [42]

➤ New Drugs:

The Department of Health & Family Welfare, in coordination with the Department of Health Research, carefully evaluated and validated newer treatment regimens for TB. This process included an in-depth review of scientific evidence by national experts. Additionally, a Health Technology Assessment was conducted to confirm that the new MDR-TB treatment approach is both safe for patients and cost-effective for public health implementation.

This move by Government of India is expected to significantly boost the country's progress to achieve its national goal of Ending TB. The Central TB Division under the Ministry of Health & Family Welfare is developing a structured, nationwide plan to introduce the BPaLM regimen within a defined timeframe. This strategy is being prepared in collaboration with States and Union Territories and includes comprehensive training programs to equip healthcare professionals with the necessary skills to safely and effectively administer the new treatment regimen.

The BPaLM regimen, which combines four medicines—Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin—has demonstrated improved safety and effectiveness compared to earlier MDR-TB treatment approaches. It also offers a shorter and faster course of therapy, making it a more efficient option for managing drug-resistant tuberculosis. [43]

• Bedaquiline:

Bedaquiline acts by targeting the ATP synthase enzyme in mycobacteria, specifically blocking the proton pump required for ATP production. It is the first drug in the diarylquinoline class and has bactericidal activity. [44][45] Since ATP is essential for cellular energy, its inhibition

quickly slows mycobacterial growth. Although the bacteria do not die immediately, sustained treatment leads to consistent bacterial cell death over the following days. [46]

- **Pretomanid:**

Pretomanid becomes active inside the mycobacterial cell through the action of a deazaflavin-dependent nitroreductase (Ddn) enzyme, which uses the reduced form of coenzyme F420. This activation generates nitric oxide and reactive metabolites. These compounds interfere with DprE2, an enzyme necessary for the production of arabinogalactan, an important component of the mycobacterial cell wall where mycolic acids attach. A similar mechanism is seen with delamanid. Resistance to pretomanid is often associated with mutations affecting the biosynthesis pathway of coenzyme F420. [47]

- **Linezolid:**

Linezolid is the first oxazolidinone antibiotic with strong activity against *Mycobacterium tuberculosis*. It works by binding to the 50S subunit of the bacterial ribosome, preventing the formation of the 70S initiation complex and thereby stopping protein synthesis at an early stage of translation. According to WHO recommendations, linezolid is an important component in treatment regimens for patients with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), as well as those with additional resistance to fluoroquinolones (pre-XDR-TB). [48]

IV. CONCLUSION

The drug utilization evaluation conducted at the District TB Center, Mehsana, highlights the importance of systematic monitoring of anti-tubercular therapy to ensure rational prescribing practices. The majority of patients were treated according to standardized national guidelines with appropriate first-line regimens for drug-sensitive TB and suitable second-line or newer regimens for resistant cases. The integration of rapid molecular diagnostics has strengthened early detection of resistance, enabling timely initiation of effective therapy. Rational use of fixed-dose combinations and weight-based dosing minimized the risk of underdosing and resistance development. Nevertheless, the rising trend incidence of MDR and XDR-TB underscores the necessity for vigilant pharmacovigilance, adherence monitoring, and continuous professional training of healthcare providers. Regular drug utilization studies are essential for improving treatment outcomes, reducing adverse effects, and supporting national efforts toward TB elimination. Strengthening patient education and follow-up mechanisms will further enhance therapeutic success and contribute to sustainable tuberculosis control strategies.

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