

Review Article

Evolution of tuberculosis treatment: from the sanatorium era to modern short-course regimens

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ABSTRACT

Tuberculosis (TB), which is a bacterial disease caused by *Mycobacterium tuberculosis*, still remains a prominent global public health challenge though it is both preventable and curable. The disease was historically managed through supportive care like the sanatorium care and collapse therapy. The treatment of TB was transformed in the antibiotic era. This was brought about by the introduction of streptomycin and the subsequent multidrug regimens. As per the World Health Organization (WHO), TB continues to affect a total of 10 million people approximately in a year, and causes 1.5 million deaths. It disproportionately poses a burden on high-incidence countries such as India. Strategies to combat TB include Directly Observed Treatment, Short-course (DOTS), the End TB Strategy, and India's National Tuberculosis Elimination Programme (NTEP). These have markedly improved diagnosis, adherence to treatment, and subsequently outcomes. Treatment success rates are now reaching nearly 88% for drug-susceptible TB. However, the rise of extensively drug-resistant (XDR-TB) and multidrug-resistant (MDR-TB) tuberculosis poses a significant concern, necessitating the adoption of new, shorter, all-oral regimens like BPaL and BPaLM that include medications like bedaquiline and pretomanid. Recent efforts include plans to make the treatment duration shorter and develop host-directed therapies aimed at enhancing immune response. This review probes into the historical evolution and present therapeutic strategies, and emerging innovations in the management of TB.

Keywords: Tuberculosis, Anti-tuberculosis treatment, Drug resistance

INTRODUCTION

Tuberculosis (TB) is a disease that has existed in ancient history and this can be evidenced by palaeopathological findings in skeletal remains.¹ The disease's causative agent was unknown until Robert Koch identified the bacillus that caused it on March 24, 1882. This bacillus was subsequently identified as *Mycobacterium tuberculosis*.² TB is an infectious and contagious disease that most frequently affects the respiratory system. It is transmitted as an air-borne infection spreading when people affected with pulmonary TB sneeze, cough or spit. According to World Health Organization (WHO), about one-fourth of the world population is likely to be infected with TB bacilli. It is also estimated that 5–10% of

infected individuals develop active disease during their entire lifetime.³

GLOBAL DISEASE BURDEN

Annually, on an average nearly 10 million people contract TB worldwide. It is estimated that 1.5 million people die from TB each year, despite the fact that the disease is preventable and curable. Because of this, TB is one of the most common infectious causes of death worldwide (Figure 1). Additionally, it is the primary cause of death for individuals living with HIV/AIDS (PLWHA) and plays a major role in the escalating issue of antimicrobial resistance (AMR). According to the WHO, most people who get affected with TB each year reside in 30 high TB

burden countries, which accounts for about 87% of the global burden in 2024.⁴ The countries which show the largest burden (almost 67%) of the disease in increasing order are: Bangladesh (3.6%), Democratic Republic of the Congo (3.9%), Nigeria (4.8%), Pakistan (6.3%), China (6.5%), Philippines (6.8%), Indonesia (10%), and India (25%).⁴

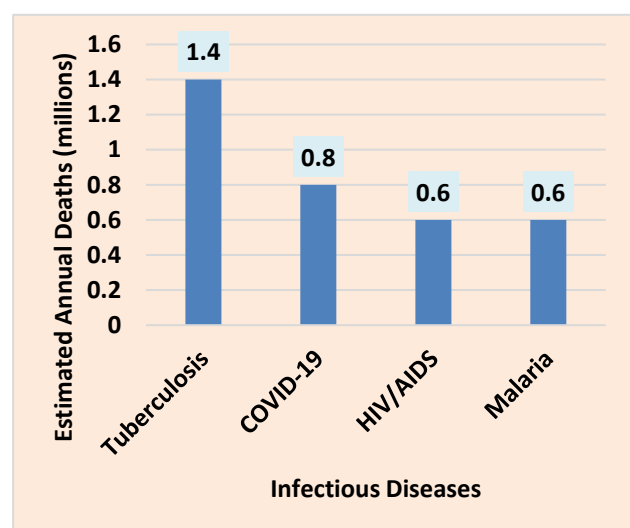


Figure 1: Global burden of major infectious diseases showing estimated annual deaths.

(Data adapted from WHO Global Tuberculosis Reports and Global Health Estimates)

Role of anti-tubercular treatment

Improvement among patients' active TB on anti-tubercular therapy (ATT) and their prognosis has been marked and profound. A 6-months and 9-months regimens have been found successful. Surgical therapy is rarely necessary.⁷ The introduction and scale-up of effective ATT has played a role in decreasing the global burden of TB. As per the WHO, the therapeutic success rate for drug-susceptible TB (DS-TB) remains high and is at about 88%. The success rate for rifampicin-resistant tuberculosis (RR-TB) has improved to about 71% in recent years. Effective treatment programs implemented globally have had a significant impact on reducing mortality. It is estimated that between 2000 and 2024, TB treatment has averted approximately 83 million deaths worldwide.⁵

WHO end TB strategy

The End TB Strategy, launched by the WHO, aims to eliminate TB as a public health problem globally by strengthening prevention, diagnosis, treatment, and research efforts (Table 1).⁵

National tuberculosis elimination programme (NTEP)

The National Tuberculosis Elimination Programme (NTEP) is a central Government of India (GoI) sponsored

National health programme (NHP) that aims to eliminate TB as a public health problem by the year 2025. This is five years ahead of the worldwide target established by the United Nations Development Programme (UNDP) under the Sustainable Development Goals (SDG). The programme focuses on early and improved case detection, universal drug susceptibility testing, patient-centred treatment, and strengthened surveillance systems. It also emphasizes digital tools such as the Nikshay portal for TB patient tracking and management, along with nutritional support through Nikshay Poshan Yojana to improve treatment adherence and outcomes.⁸

Table 1 Key targets of end TB strategy.⁵

Components	Description
Goal	End the Global Tuberculosis epidemic
Target year	2035
Reduction in Deaths due to TB	95% reduction as compared with 2015
Reduction in Incidence of TB	90% reduction as compared with 2015
Catastrophic costs for TB Patients	0% of TB-affected families facing catastrophic costs

Drug resistance tuberculosis

Drug-resistance tuberculosis (DR-TB) remains a major critical public health issue worldwide. Rifampicin is the most effective 1st line anti-TB drug but its resistance is of particular concern. Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to both isoniazid and rifampicin. Both MDR-TB and rifampicin-resistant tuberculosis (RR-TB) require treatment with 2nd line anti-tubercular drugs such as fluoroquinolones.⁵

In the year 2024, more than 50% of the global MDR/RR-TB cases occurred in four nations: India (32%) which contributed the most followed by, China (7.1%), Philippines (7.1%), and Russia (6.7%). The highest proportions of DR-TB among previously treated patients are reported in Central Asia and Eastern Europe.⁵

In order to support international efforts to control and eliminate TB, this review looks at the history of TB therapy and emphasize current developments, new drug-resistant problems, and potential therapeutic approaches.

METHODS

A comprehensive literature search was carried out using electronic databases such as PubMed and Google Scholar, along with official reports from the World Health Organization (WHO). Relevant articles were identified using keywords such as "tuberculosis," "history of tuberculosis," "BCG vaccine," "antitubercular therapy," "drug-resistant tuberculosis," and "global tuberculosis burden." Boolean operators (OR, AND) were applied to refine this search. Filters including English language and

availability of full-text articles were applied. In addition, landmark studies, WHO reports, and national program documents related to tuberculosis were also included. Studies were included if they focused on epidemiology, historical evolution, prevention, or treatment of tuberculosis. Articles not relevant to the topic or lacking sufficient scientific quality were excluded. The selected literature was reviewed and synthesized to present a comprehensive overview of tuberculosis under thematic headings.

EVOLUTION OF TUBERCULOSIS TREATMENT

Pre-antibiotic era treatment of tuberculosis

Sanatorium treatment

In the second century BCE, Galen recommended fresh air, milk, and sea voyages for the treatment of phthisis, and individuals with scrofula were treated with the royal touch throughout the mid ages.¹ The first widely accepted approach to TB treatment in the pre-antibiotic era was the sanatorium cure, first described in 1854 by Hermann Brehmer. After recovering from TB during travel to the Himalayan Mountains, Brehmer proposed that the disease could be treated through exposure to fresh air, adequate nutrition, and rest. He later established a sanatorium in Görbersdorf, where patients were treated in a mountain environment with continuous exposure to fresh air and improved diet. This model became widely adopted, and many sanatoria were established across Europe and North America, helping treat numerous TB patients during the late nineteenth and early twentieth centuries.¹

In 1865, Jean Antoine Villemin demonstrated that TB was an infectious disease. His observations showed that TB occurred more frequently among soldiers living in crowded barracks than among those stationed in open fields. He also noted that healthy recruits from rural areas often developed TB after several months of military service, supporting the idea that TB spreads through transmission in close living conditions.²

Collapse therapy

Collapse therapy was widely used in the early twentieth century as a treatment for pulmonary TB. The principle of collapse therapy was to intentionally collapse the affected lung or reduce its movement so that the diseased lung tissue could rest and heal. This approach was also believed to reduce the oxygen supply to *Mycobacterium tuberculosis*, which thrives in oxygen-rich environments. Several techniques were used, including artificial pneumothorax, in which air was introduced into the pleural cavity to collapse the lung; pneumoperitoneum, which elevated the diaphragm and limited lung expansion; phrenic nerve crush, which reduced diaphragmatic movement; and thoracoplasty, a surgical procedure involving removal of ribs to permanently collapse the affected lung area. Although these methods

sometimes improved symptoms and slowed disease progression, they were invasive and associated with significant complications. The use of collapse therapy gradually declined after the discovery of effective anti-TB drugs.⁹

Bacillus Calmette–Guérin vaccine

The Bacillus Calmette–Guérin (BCG) is the only currently available vaccine for the prevention of TB and has been widely used since its introduction in 1921. It was developed by Camille Guérin and Albert Calmette. It was developed using an attenuated *Mycobacterium bovis* strain. It protects infants and young children against severe types of TB. Evidence suggests that BCG provides approximately 70–80% protection against severe childhood TB particularly tuberculous meningitis and miliary TB. However, its efficacy against pulmonary TB is highly inconsistent, ranging from 0–80% across different populations (Figure 2). Systematic reviews have demonstrated approximately 19–27% protection against infection and about a 50% reduction in TB disease risk. Protection is generally strongest in neonates and young children and may persist for several decades.¹⁰

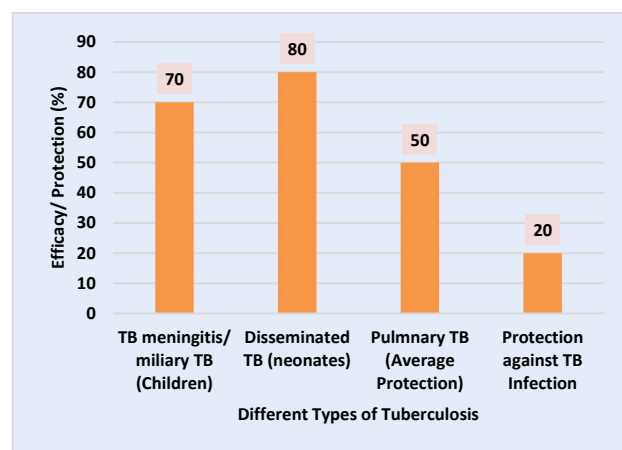


Figure 2: Efficacy of BCG Vaccine against Different TB Outcomes.¹⁰

Limitations associated with pre-antibiotic era treatment strategies

Before the discovery of effective anti-TB drugs, treatment strategies such as sanatorium care, nutritional therapy, and collapse therapy were largely supportive rather than curative. The absence of antimicrobial agents capable of eliminating *Mycobacterium tuberculosis* resulted in low cure rates and high mortality. Patients often required prolonged hospitalization in sanatoria for months or even years, which was costly and impractical. Additionally, invasive procedures such as thoracoplasty, artificial pneumothorax, and phrenic nerve crush were associated with significant complications. Access to treatment was also limited because sanatorium care required specialized facilities.¹¹

Antibiotic era

The antibiotic era of TB treatment began in the 1940s with the discovery of effective anti-TB drugs, which dramatically transformed TB management. The first major breakthrough came with the advent of streptomycin in 1943 by Selman Waksman and his colleagues. Streptomycin was the first antibiotic shown to be effective against *Mycobacterium tuberculosis* and significantly improved survival rates among patients with TB. However, it was soon observed that streptomycin monotherapy led to rapid development of drug resistance.¹²

Para-amino salicylic acid (PAS) was introduced in 1949, followed by isoniazid in 1952, which proved to be a highly potent bactericidal drug against *Mycobacterium tuberculosis*. Over the following decades, further advances occurred with the introduction of ethambutol in 1961, rifampicin in 1966, and pyrazinamide becoming widely adopted in the 1970s. These developments ultimately led to the establishment of the standardized HRZE regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol, which forms the backbone of modern TB chemotherapy.¹²

Under the current guidelines of WHO, treatment of DS-TB is based on a six-month short-course regimen divided into two phases. The intensive phase (IP) consists of HRZE administered for the first two months, during which the bacterial load is rapidly reduced and transmission risk declines. This is followed by a continuation phase (CP) that includes administration of isoniazid and rifampicin for a period of four months. This is aimed at eliminating persistent bacilli and preventing relapse. The HRZE combination is effective because each drug targets the pathogen through different mechanisms and metabolic stages, thereby enhancing bactericidal activity while preventing the emergence of resistance. The adoption of HRZE chemotherapy significantly improved cure rates, reducing treatment duration, and enabled TB management to transition from prolonged sanatorium-based care to effective outpatient treatment facilities.¹³

Directly observed treatment, short-course

The Directly Observed Treatment, Short-course (DOTS) strategy was introduced by the WHO in the early 1990s and was officially recommended in 1994 to strengthen global TB control. The strategy emphasized standardized treatment regimens, direct supervision of therapy, and strong health system support to improve treatment adherence and patient outcomes. The implementation of DOTS significantly improved treatment success rates and contributed to reductions in TB related mortality in many high-burden countries.¹⁴

DOTS strategy consists of five components: which include the political and administrative commitment,

good quality diagnosis primarily by sputum smear microscopy and other microbiological tools, uninterrupted supply of good quality anti-TB drugs, directly observed treatment (DOT) and systematic monitoring and accountability.¹⁴

Multidrug-resistant Tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by strains resistant to both rifampicin and isoniazid, while rifampicin-resistant tuberculosis (RR-TB) refers to resistance to rifampicin with or without resistance to other anti-TB drugs.⁴

Although treatment outcomes have improved over time, success rates remain relatively low. The global treatment success rate for MDR/RR-TB was 63% in 2020, compared with 60% in 2019 and 50% in 2012. The spread and emergence of MDR/RR-TB are primarily attributed to mismanagement of TB therapy and ongoing person-to-person transmission. Factors such as inappropriate drug regimens, use of poor-quality medications, single drugs, inadequate storage conditions, and premature interruption of treatment contribute to the development of drug resistance. Once resistance develops, resistant strains can spread through airborne transmission, particularly in crowded environments such as hospitals, prisons, and densely populated communities.⁴

Management of MDR/RR-TB has considerably evolved with guidelines from the WHO that recommend all-oral and shorter treatment regimens. The 6-month BPaLM regimen that consists of bedaquiline, pretomanid, linezolid, and moxifloxacin is considered a preferred regimen. In cases of confirmed fluoroquinolone resistance, moxifloxacin may be omitted. Another recommended option is the all-oral regimen which is given for 9-months, which includes bedaquiline in combination with fluoroquinolones (moxifloxacin and levofloxacin), clofazimine, pyrazinamide, ethambutol, high-dose isoniazid, and ethionamide or linezolid. These evolving treatment strategies reflect ongoing efforts to improve treatment outcomes and control the global burden of DR-TB.¹¹

Extensively drug-resistant tuberculosis

The updated definition of XDR-TB refers to TB caused by strains that fulfil the definition of MDR/RR-TB and are additionally resistant to any fluoroquinolone and at least one Group A drug, such as bedaquiline or linezolid, which are among the most potent second-line anti-TB medicines.¹³

According to estimates from the WHO, nearly 470,000 people develop MDR/RR-TB each year, and approximately 180,000 deaths occur due to this form of TB annually. (Figure 3) Worldwide, among a total of 105 countries with representative data, about 20% of people with MDR/RR-TB also have resistance to a

fluoroquinolone which is one of the most important drugs used for the treatment of DR-TB. XDR-TB represents a more severe form of MDR-TB and is associated with not so good treatment outcomes and poor prognosis.⁴

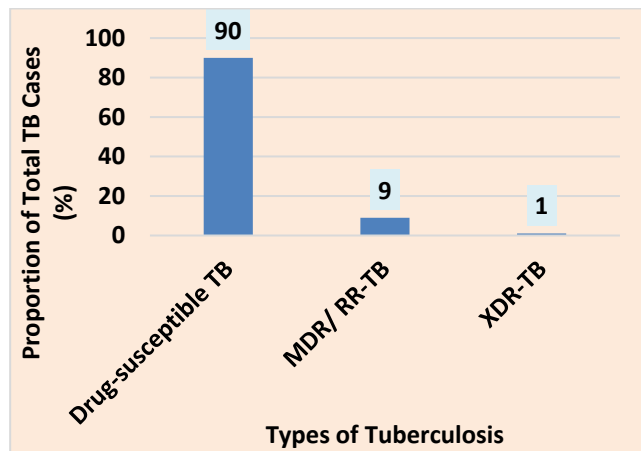


Figure 3: Global Burden of Drug-Susceptible, MDR and XDR-TB.⁴

RECENT ADVANCES IN TUBERCULOSIS TREATMENT

In the recent years, the treatment and prophylaxis of TB have seen significant advancements particularly with the advent of new ATT drugs, repurposed medications, and shorter treatment regimens that are aimed at improving patient outcomes.

One of the most important developments in recent years has been the introduction of newer ATT drugs such as Bedaquiline and Pretomanid, along with the repurposing of drugs such as linezolid. The mode of action of Bedaquiline is by inhibiting ATP synthase enzyme, thereby disrupting the energy production of *TB Bacilli*.¹⁶ Pretomanid is a nitroimidazooxazine drug. This drug acts by inhibiting synthesis of mycolic acid resulting in defective cell wall formation. This leads to bacterial cell death. It is found to be active against both non-replicating and replicating TB bacilli.¹⁷ Linezolid, which is another new drug is the first oxazolidinone approved for clinical use, has been effective *in vitro* and shows considerable promise *in vivo* activity against *TB bacilli*. Linezolid has early bactericidal activity against rapidly dividing tubercle bacilli in patients with cavitary pulmonary TB.¹⁸

The development of new combination regimens has further transformed the management of DR-TB. Regimens such as BPaL (bedaquiline, pretomanid, and linezolid) and BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin) have shown promising results in the treatment of MDR-TB and XDR-TB. These regimens are particularly significant because they can reduce the duration of therapy to approximately six months, compared with traditional MDR-TB treatment regimens that often required 18–24 months of therapy and

included injectable drugs associated with severe adverse effects.¹³

Additionally, the use of higher-dose rifamycin and optimized drug combinations for DS-TB is being explored. Several studies are evaluating the possibility of shortening treatment duration from the traditional six-month regimen to four months without compromising treatment efficacy.¹³

Newer shorter regimens

Recent advances in TB treatment have given emphasis on developing more effective treatment with shorter regimens to improve patient adherence and treatment outcomes. The WHO has recommended several shorter regimens for both DS and DR-TB.

A 4-month regimen (isoniazid, rifapentine, moxifloxacin, and pyrazinamide) for the treatment of DS-TB.¹³

A 6-month BPaLM regimen (bedaquiline, pretomanid, linezolid, and moxifloxacin) for patients with MDR/RR-TB.¹³

Evidence from a clinical trial conducted by Dorman SE et al demonstrated that a 4-month rifapentine–moxifloxacin regimen was non-inferior to the standard 6-month treatment regimen for pulmonary tuberculosis.¹⁵

DISCUSSION

This thorough review explains the evolution of TB treatment from the mostly supportive pre-antibiotic approaches, such as collapse therapy and sanatorium care, to the more revolutionary multidrug chemotherapy of the present day. (Figure 4)

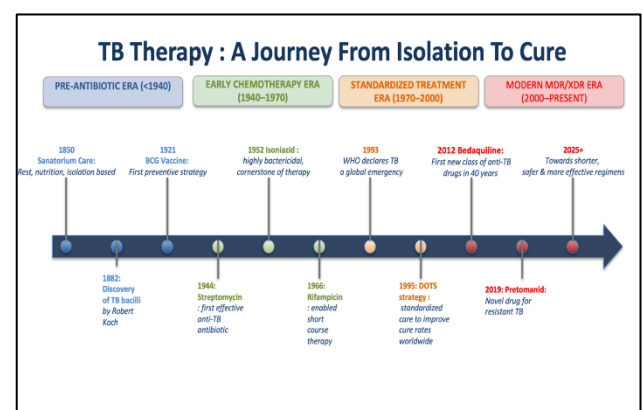


Figure 4: Evolution of TB treatment.

A significant and noteworthy fact is that the sequential discovery of anti-TB medications, such as streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, led to the standardized HRZE regimen and the DOTS strategy, which together increased DS-TB treatment success rates to about 88% and prevented an estimated 83

million deaths between 2000 and 2024.^{4,5} This review's key strength is its comprehensive synthesis of historical and modern data, which offers contextual understanding of how each therapeutic era built upon the shortcomings of the previous one. However, as it is a narrative review, selection bias and the lack of thorough meta-analytic techniques make its conclusions regarding comparative efficacy less reliable. The effectiveness of the BCG vaccination against pulmonary TB varies greatly among communities (0–80%), which has led to continuous discussion regarding the vaccine's use in adult immunization programs.¹⁰ The most urgent interpretive concern is the emergence of MDR-TB and XDR-TB: drug resistance is a result of both systemic failures in treatment adherence and drug supply, highlighting the paradox at the core of TB control, and previous treatment success, which drives widespread use of rifampicin and isoniazid.

An important area of research in TB management is host-directed therapy (HDT), which focuses on enhancing the host immune response rather than directly targeting *Mycobacterium tuberculosis*. These therapies aim to modulate the immune system to reduce excessive inflammation and tissue damage while improving bacterial clearance. By targeting host pathways involved in the immune response, HDT has the potential to improve treatment effectiveness and may contribute to shortening the duration of conventional ATT when used alongside standard drug regimens.¹⁶

Several host-directed therapeutic approaches are currently under investigation, including the use of immunomodulatory agents, anti-inflammatory drugs, statins, and therapeutic vaccines. These strategies may help improve treatment outcomes, particularly in patients with drug-resistant tuberculosis. Ongoing clinical trials continue to evaluate the safety and efficacy of these approaches, offering promising prospects for future tuberculosis treatment.¹⁶

Ultimately, as the conclusion reflects, ending the TB epidemic will demand not only continued pharmacological innovation but also sustained investment in equitable access, surveillance, and prevention infrastructure globally.

Despite these developments, the emergence of XDR and MDR-TB has created new challenges to global TB control. Recent developments have significantly improved treatment outcomes for DR-TB, including new anti-TB medications, shortened all-oral therapy regimes, and improved diagnostic tools. Additionally, there are exciting opportunities to improve preventative and therapeutic efforts through ongoing research into new vaccines, host-directed therapies, and distinctive drug combinations.

The developments in TB treatment represent continued scientific advancements and global public health

campaigns. In order to achieve the goal of ending the TB epidemic in the coming decades, it will be essential to improve research, increase access to effective medications, and improve prevention initiatives.

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