Tuberculosis: Epidemiology, Pathogenesis, Diagnosis, and Treatment in the Modern Era

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Abstract

Background: Tuberculosis (TB) remains one of the most significant infectious diseases globally, responsible for high morbidity and mortality despite being preventable and curable. Advances in science and medicine have improved our understanding of TB epidemiology, pathogenesis, and management, yet challenges such as drug resistance, HIV co-infection, and health system constraints persist. This review aims to provide a comprehensive overview of TB in the modern era, addressing its epidemiology, risk factors, etiology, virulence mechanisms, pathophysiology, clinical spectrum, diagnostic modalities, and treatment strategies. Emphasis is placed on both global perspectives and regional contexts, including intermediate-burden countries such as Egypt. Evidence highlights that TB remains concentrated in low- and middle-income countries, though migration and social determinants sustain its presence in high-income regions. The disease's pathogenesis is shaped by complex host–pathogen interactions, granuloma biology, and immune evasion. Clinically, TB manifests as pulmonary, extrapulmonary, or disseminated disease, with significant diagnostic challenges. While molecular assays and novel biomarkers have enhanced detection, access remains unequal. Standard six-month therapy for drug-susceptible TB remains effective, but drug-resistant TB requires newer, longer, and often toxic regimens. Preventive therapy for latent TB infection is critical for high-risk populations.

Conclusion: Despite progress, TB elimination remains off-track due to persistent socioeconomic determinants, health system gaps, and biological complexity. Continued innovation in diagnostics, therapeutics, and vaccines, combined with strong political and health system commitments, are essential to achieve the global goal of ending TB as a public health threat.

Keywords: *Tuberculosis, epidemiology, pathogenesis, diagnosis, treatment, drug resistance, Egypt*

Introduction

Tuberculosis (TB) remains a major global health threat, responsible for considerable morbidity and mortality despite being both preventable and curable. Caused by members of the *Mycobacterium tuberculosis* complex and transmitted via inhalation of infectious droplet nuclei, TB exhibits a prolonged natural history and complex host–pathogen interactions that challenge control efforts in diverse settings. Its burden concentrates in low- and middle-income countries, yet it is present worldwide and continues to demand sustained public health attention. [1,2]

Following exposure to *M. tuberculosis*, outcomes range from sterilizing immunity to persistent infection that can remain clinically silent or progress along a continuum from incipient and subclinical states to active disease. The term "TB infection" (TBI) increasingly replaces "latent TB" to reflect this dynamic spectrum and the absence of definitive tools to demarcate latency from very early disease. Immune containment within granulomas explains long periods of quiescence, whereas breakdown under conditions such as immunosuppression, malnutrition, or co-infections enables reactivation and transmission. [3–6]

Recent years have seen parallel challenges and advances. COVID-19 disrupted TB services and surveillance, but it also accelerated innovation in diagnostics and program delivery that can be leveraged for TB. Molecular tests (e.g., Xpert MTB/RIF Ultra), improved imaging algorithms, and updated guidance for diagnosing TB infection have strengthened the diagnostic armamentarium, although access gaps persist. At the same time, drug-resistant TB and co-morbidities (HIV, diabetes) complicate management and underscore the need for integrated, resilient strategies spanning prevention, early detection, and effective therapy. [7–10]

History of Tuberculosis

Tuberculosis (TB) is one of the oldest known human diseases, with evidence of its presence dating back thousands of years. Skeletal remains of Egyptian mummies from 2400 BC demonstrate characteristic deformities such as Pott's disease, indicating spinal tuberculosis. Similarly, ancient Indian and Chinese texts describe conditions resembling TB, while art and records from early civilizations depict its crippling skeletal manifestations. These findings establish TB not only as an ancient affliction but also as one that has shaped human history through its social and cultural footprint. [11,12]

In medieval Europe, TB was widely referred to as "consumption" due to the severe wasting it caused in patients. The cervical lymphadenitis form of TB was known as scrofula, or the "king's evil," and was thought to be curable by the royal touch in England and France. During this period, TB was considered a hereditary or constitutional disease rather than an infectious one, reflecting the limited understanding of its etiology. The sanatorium movement of the 18th and 19th centuries, emphasizing fresh air, nutrition, and rest, was one of the first structured public health responses to TB and remained in use until more effective therapies were developed. [13,14]

A major turning point came in 1720, when Benjamin Marten suggested the possibility that TB was caused by "minute living creatures." However, it was not until Robert Koch's groundbreaking discovery in 1882 that *Mycobacterium tuberculosis* was definitively identified as the causative agent. Koch's work in staining, culturing, and reproducing the disease in animals established TB as a bacterial infection and earned him the Nobel Prize in Medicine in 1905. His findings not only transformed TB management but also advanced the broader germ theory of disease, influencing modern microbiology and infectious disease control. [15,16]

Following Koch's discovery, a wave of scientific progress unfolded. The early 20th century saw the development of the tuberculin skin test by Charles Mantoux, which provided a method for detecting TB infection in asymptomatic individuals. Later, in 1921, Calmette and Guérin introduced the Bacillus Calmette-Guérin (BCG) vaccine, the first and only licensed vaccine for TB to date, which remains widely used in high-burden countries to protect children against severe forms of the disease. The mid-20th century brought the discovery of streptomycin and other effective antimicrobials, revolutionizing

treatment and marking the beginning of antibiotic therapy against TB. [17–19]

Despite these advances, TB has continued to resurge at different points in history, often influenced by social, economic, and epidemiological changes. The 20th century was marked by a dramatic decline in TB incidence in many high-income countries due to the combined effects of vaccination, antimicrobial therapy, and improved living conditions. However, the disease remained entrenched in low- and middle-income regions, where poverty, undernutrition, and overcrowding created fertile ground for transmission. In recent decades, the HIV/AIDS epidemic and the emergence of multidrug-resistant TB (MDR-TB) have reversed many earlier gains, re-establishing TB as a top global health threat in the 21st century. [20,21]

Epidemiology of Tuberculosis

Tuberculosis remains one of the leading causes of infectious disease mortality worldwide, despite substantial progress in diagnostic tools, vaccines, and treatment. According to the World Health Organization (WHO) Global TB Report 2023, an estimated 10.6 million people fell ill with TB in 2022, with 1.3 million deaths among HIV-negative individuals and 167,000 deaths among people living with HIV. These numbers highlight that TB, unlike many other infectious diseases, continues to exert a disproportionately high burden on low- and middle-income countries (LMICs), particularly in Sub-Saharan Africa and South-East Asia. [22]

Globally, TB is present in every country, but its distribution is uneven. Nearly 70% of all TB cases occur in just 30 high-burden countries, with India, Indonesia, China, the Philippines, Pakistan, Nigeria, and Bangladesh accounting for more than half of all cases. This concentration reflects a combination of socioeconomic inequalities, limited healthcare infrastructure, and co-morbid conditions that drive ongoing transmission. By contrast, high-income countries have seen TB incidence decline steadily over the past century, with some regions approaching elimination. However, challenges remain in these settings due to migration, delayed diagnosis, and clusters of drug-resistant TB. [23,24]

The global epidemiology of TB is further shaped by the HIV epidemic, which remains a significant driver of incidence and mortality. People living with HIV are estimated to have an 18-fold increased risk of developing active TB compared to HIV-negative individuals. In regions such as Sub-Saharan Africa, where both diseases are prevalent, HIV–TB co-infection contributes to high mortality rates and complicates disease management. Additionally, the rise in non-communicable conditions such as diabetes mellitus, which triples the risk of progression from latent TB infection to active disease, is increasingly recognized as an emerging threat in TB epidemiology. [25–27]

The COVID-19 pandemic created further disruption in TB epidemiology. During 2020, TB case notifications dropped by 18% globally due to restrictions on health services and the diversion of resources to COVID-19 response. Although TB incidence appears to have rebounded somewhat in 2021–2022, the pandemic erased several years of progress, delaying the global End TB Strategy targets. This setback was particularly pronounced in LMICs, where healthcare systems faced overwhelming strain. Modeling studies suggest that millions of additional TB deaths could occur in the coming years due to diagnostic and treatment delays induced by the pandemic. [28,29]

Egypt represents a country with an intermediate TB burden. According to WHO estimates, the incidence of TB in Egypt is approximately 12 cases per 100,000 population, a relatively modest figure compared to neighboring African countries. However, disparities exist between governorates, with higher burdens noted in densely populated regions such as Cairo, Giza, and Sharqia. National TB control efforts in Egypt have been challenged by underdiagnosis, treatment adherence issues, and healthcare resource constraints, though progress has been made with the expansion of DOTS (Directly Observed Treatment, Short-course) and integration of molecular diagnostics. [30,31]

In low-incidence countries such as the United States, TB control has advanced significantly, with annual case counts declining for nearly three decades. Between 1995 and 2014, U.S. TB prevention programs were estimated to have prevented nearly 300,000 cases and saved billions of dollars in healthcare costs. However, in 2020, coinciding with the COVID-19 pandemic, TB case counts dropped abruptly due to

underdiagnosis, followed by increases in 2021 and 2022 as delayed cases were detected. This experience underscores how epidemiology is sensitive not only to underlying biological drivers but also to disruptions in health systems and surveillance. [32,33]

Despite remarkable progress in some regions, TB elimination remains a distant goal for many parts of the world. The WHO End TB Strategy, which set ambitious targets for 2030 and 2035, is off-track, largely due to persistent social determinants such as poverty, malnutrition, and limited healthcare access. The persistence of TB highlights the critical interplay between biomedical advances and socioeconomic development, emphasizing that TB control is inseparable from broader efforts to improve equity and strengthen health systems. [34,35]

Risk Factors for Tuberculosis Infection

The risk of acquiring tuberculosis begins with exposure to an infectious case, but not all exposures lead to infection or disease. Multiple determinants—including biological, environmental, and social factors—influence the trajectory from exposure to latent TB infection (LTBI) and, ultimately, progression to active TB disease. Prolonged and close exposure to a highly infectious index case is one of the most significant risk factors. Patients with smear-positive, cavitary pulmonary TB excrete large numbers of bacilli, and household contacts of such individuals are consistently found to have the highest rates of infection, irrespective of the background community incidence. [36]

Environmental conditions further shape risk. Overcrowded living environments, poor ventilation, and shared airspace in institutions such as prisons, shelters, or healthcare facilities amplify the probability of airborne transmission. This is particularly critical in low-income urban settings, where dense housing and limited infrastructure create conditions conducive to the spread of TB. The risk is magnified in populations already marginalized by poverty, unemployment, or displacement, underscoring TB's role as both a biomedical and a social disease. [37,38]

Biological factors also play a pivotal role in determining susceptibility. Immunosuppression, whether due to HIV infection, malnutrition, or iatrogenic causes such as corticosteroid therapy, significantly increases the likelihood of progression from LTBI to active disease. Among these, HIV remains the most potent risk factor, with co-infected individuals facing an annual risk of 10% for developing active TB—compared to a lifetime risk of 5–10% in immunocompetent individuals. Other conditions such as diabetes mellitus, chronic kidney disease, and malignancies also impair host immunity and raise the risk of TB reactivation. [39–41]

Children represent another vulnerable group due to their immature immune responses. Pediatric TB often reflects recent transmission and can progress rapidly to severe forms such as miliary TB or TB meningitis. Co-infections with viruses, such as cytomegalovirus or respiratory syncytial virus, may further compromise immune control in children. Conversely, routine childhood vaccination, including Bacillus Calmette-Guérin (BCG), provides some protection against disseminated TB, though its efficacy against pulmonary disease in adults remains variable. [42,43]

Lifestyle and behavioral factors also modify risk. Cigarette smoking is strongly associated with TB infection and progression, as smoke damages mucociliary clearance, impairs macrophage function, and induces structural lung disease. Alcohol misuse and substance use disorders are similarly linked to increased TB risk, primarily through immune suppression and poor treatment adherence. Urban indoor air pollution, particularly from biomass fuels and poor ventilation, has been implicated as an important contributor to TB transmission and infection in children and adults. [44,45]

Importantly, migration and mobility affect TB epidemiology and risk at the individual and community level. Migrants from high-burden countries often carry LTBI to low-incidence countries, where reactivation can contribute disproportionately to national TB case counts. Barriers such as limited healthcare access, language difficulties, and stigma often delay diagnosis and treatment, perpetuating transmission. Addressing TB in migrants requires tailored approaches that combine early screening, preventive therapy, and culturally sensitive care models. [46]

Overall, the interplay between host, pathogen, and environment defines the risk of TB infection and

progression. Recognizing and addressing these risk factors is essential not only for clinical management but also for achieving global TB elimination targets. By integrating biomedical interventions with social and structural reforms, it may be possible to interrupt transmission and reduce the burden of disease in vulnerable populations. [47]

Etiology of Tuberculosis

Tuberculosis is caused by members of the *Mycobacterium tuberculosis* complex (MTBC), a closely related group of acid-fast bacilli that infect humans and animals. The principal agent is *Mycobacterium tuberculosis* (Mtb), which accounts for the vast majority of human TB cases worldwide. Other members of the complex include *M. africanum*, which causes human disease primarily in West Africa, and zoonotic species such as *M. bovis*, *M. caprae*, and *M. pinnipedii*, which infect both animals and humans. Although less common, zoonotic transmission from livestock or wildlife reservoirs continues to pose challenges in certain endemic areas, especially where bovine TB remains uncontrolled. [48,49]

Transmission occurs when an individual with active pulmonary or laryngeal TB expels bacilli in droplet nuclei during coughing, sneezing, shouting, or singing. These droplet particles, measuring 1–5 microns, can remain airborne for prolonged periods and penetrate deep into the alveoli of exposed contacts. The probability of transmission depends on factors such as bacillary load in the index case, duration and intensity of exposure, and environmental ventilation. Notably, individuals with smear-positive pulmonary TB and cavitary lung lesions are the most infectious, accounting for the majority of new transmissions. [50,51]

Once inhaled, *M. tuberculosis* bacilli encounter the innate immune defenses of the lung. Alveolar macrophages phagocytose the bacilli, but Mtb possesses remarkable adaptations that enable survival within these cells. The pathogen prevents phagosome–lysosome fusion, resists oxidative stress, and manipulates host cell signaling, allowing it to persist within macrophages. In some individuals, immune responses successfully eradicate the infection, but in others, the bacilli survive in a dormant state, establishing latent infection that can persist for decades. [52,53]

The progression from infection to disease reflects a complex balance between host immunity and bacterial virulence. Only about 5–10% of infected individuals will develop active TB during their lifetime, though this risk rises dramatically in the context of immunosuppression, malnutrition, or co-morbidities such as diabetes. The remainder harbor latent bacilli contained within granulomas, which may break down years later to cause reactivation. This capacity for latency and delayed reactivation underscores why TB continues to persist despite effective therapies, distinguishing it from many other bacterial infections. [54,55]

Importantly, molecular studies have revealed that MTBC strains exhibit genetic diversity influencing transmissibility, immune evasion, and drug susceptibility. For example, *M. africanum* demonstrates reduced transmissibility compared to Mtb, while certain Beijing lineage strains are associated with higher rates of drug resistance and relapse. These lineage-specific differences highlight the need to integrate molecular epidemiology into TB control strategies, as regional strain variation may impact clinical outcomes and public health approaches. [56,57]

In summary, TB etiology reflects a dynamic interaction between a uniquely adapted pathogen and its human host. The evolutionary success of Mtb lies in its ability to persist silently within hosts, evade immune destruction, and exploit opportunities for transmission under conditions of social and biological vulnerability. Understanding these mechanisms is fundamental to designing better preventive, diagnostic, and therapeutic interventions to disrupt the cycle of transmission and disease. [58]

Virulence Factors of *Mycobacterium tuberculosis*

The persistence and pathogenicity of *Mycobacterium tuberculosis* (Mtb) are largely determined by its wide array of virulence factors, which allow the bacillus to invade, survive, and replicate within the host. These factors can be broadly categorized into structural components, non-protein molecules such as lipids and glycolipids, and specialized proteins that modulate host immune responses. Together, they explain the ability of Mtb to establish chronic infections, resist clearance, and drive the

immunopathology characteristic of tuberculosis. [59]

Non-Protein Virulence Factors

The cell wall of Mtb is a major contributor to its virulence, comprising approximately 60% lipids. This lipid-rich structure not only provides a formidable barrier against host defenses and antibiotics but also interacts with host immune cells to modulate responses. Mycolic acids, lipoarabinomannan (LAM), and trehalose dimycolate (cord factor) are among the most studied non-protein factors. Cord factor, for instance, is directly implicated in the granulomatous response, inducing caseation necrosis that both walls off infection and contributes to tissue damage. LAM, on the other hand, interferes with macrophage activation and antigen presentation, dampening protective immunity. [60,61]

Other glycolipids such as phosphatidylinositol mannosides (PIMs) and sulfolipids further contribute to immune evasion by modulating cytokine production and disrupting phagosome maturation. These molecules collectively enable Mtb to manipulate the host environment in ways that favor bacterial survival while limiting effective clearance. Importantly, non-protein virulence factors are also considered potential biomarkers for diagnosis, with urinary LAM assays already used in patients with HIV-associated TB. [62,63]

Protein Virulence Factors

In addition to lipids, Mtb expresses a diverse proteome that plays critical roles in virulence and immune modulation. The PE and PPE protein families, characterized by proline-glutamic acid repeats, are unique to mycobacteria and are thought to alter antigen presentation, vary surface antigens, and interfere with host recognition. Lipoproteins and secretory proteins such as ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein-10) are central to Mtb pathogenicity. ESAT-6, secreted via the ESX-1 secretion system, disrupts phagosomal membranes, allowing bacilli to escape into the cytosol and spread between cells. CFP-10 synergizes with ESAT-6, enhancing host cell lysis and immune modulation. [64–66]

Additional proteins such as Ag85 complex (Ag85A, B, and C) play dual roles in cell wall synthesis and immune stimulation. These proteins facilitate the production of mycolyl-arabinogalactan–peptidoglycan, essential for maintaining Mtb's thick cell envelope, while simultaneously eliciting strong immune responses, making them leading candidates for TB vaccine development. Heat-shock proteins and enzymes such as catalase-peroxidase (KatG) also enhance Mtb survival by neutralizing reactive oxygen and nitrogen species generated by host defenses. [67,68]

Host–Pathogen Interactions

The interaction of these virulence factors with host cells ultimately shapes TB pathogenesis. By combining immune evasion, induction of granulomatous inflammation, and manipulation of host cell death pathways, Mtb creates a niche in which bacilli can persist for years. For instance, ESAT-6 and CFP-10 promote necrotic rather than apoptotic cell death, favoring bacterial dissemination. Similarly, modulation of autophagy and inhibition of phagosome–lysosome fusion allow bacilli to remain protected within host cells. These strategies underline why Mtb is exceptionally successful at establishing chronic infection and why eradication remains so challenging. [69]

In recent years, advances in genomics and proteomics have deepened our understanding of Mtb virulence. Comparative studies of different Mtb lineages reveal that virulence profiles may vary, with some strains demonstrating enhanced immune evasion and transmission potential. This knowledge is being leveraged to design novel diagnostics, therapeutics, and vaccines that specifically target virulence mechanisms rather than just bacterial replication, offering promising strategies for future TB control. [70]

Pathophysiology of Tuberculosis

The pathophysiology of tuberculosis (TB) reflects the complex interplay between *Mycobacterium tuberculosis* (Mtb) and host immune defenses. Following inhalation of infectious droplets, bacilli deposit in the alveoli where they are phagocytosed by resident macrophages. Instead of being eliminated, Mtb often survives and multiplies within these cells due to its ability to block phagosome–lysosome

fusion and resist oxidative stress. This initial stage sets the foundation for either clearance, containment, or progression to active disease. [71]

Granuloma Formation

A hallmark of TB pathophysiology is the granuloma, a structured immune aggregate that forms around infected macrophages. Granulomas are composed of epithelioid cells, multinucleated giant cells, lymphocytes, and a necrotic core. Their purpose is to contain infection and limit bacterial dissemination, but paradoxically, granulomas also provide a niche where bacilli can persist in a dormant state. The hypoxic and nutrient-limited environment of granulomas induces Mtb to enter a non-replicating state, contributing to latent infection. Over time, granulomas may undergo caseous necrosis, liquefaction, and cavitation, events that facilitate bacterial escape into airways and enhance transmission. [72,73]

Latency and Reactivation

Latent TB infection (LTBI) occurs when the host immune system contains but does not eradicate Mtb. Approximately one-quarter of the global population harbors latent infection, with most never progressing to active disease. However, factors such as HIV infection, diabetes mellitus, malnutrition, or immunosuppressive therapy significantly increase the risk of reactivation. In these cases, impaired cellular immunity allows dormant bacilli to resume replication, leading to active pulmonary or extrapulmonary TB. This ability to persist for decades and later reactivate explains why TB elimination remains elusive despite effective treatments. [74,75]

Tissue Damage and Disease Manifestation

The clinical manifestations of TB are driven not only by bacterial replication but also by the host immune response. Cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) are essential for controlling infection but can also contribute to tissue injury when dysregulated. The necrotizing inflammation within granulomas damages lung parenchyma, leading to cavitary lesions that compromise respiratory function and act as reservoirs for transmission. In extrapulmonary TB, bacilli disseminate hematogenously, causing involvement of lymph nodes, pleura, bones, meninges, and other organs. [76,77]

Immune Evasion and Chronicity

Mtb employs several strategies to evade immune clearance, prolonging its survival within the host. These include inhibition of antigen presentation, modulation of macrophage apoptosis, and suppression of autophagy. Moreover, Mtb antigens stimulate regulatory T cells and anti-inflammatory cytokines, blunting protective immunity. The result is a chronic balance where the host prevents overwhelming disease but fails to achieve sterilizing immunity, allowing Mtb to persist indefinitely. This unique equilibrium distinguishes TB from many acute infections and underpins its global persistence. [78]

Implications for Public Health

Understanding TB pathophysiology has significant implications for diagnosis, treatment, and vaccine development. The biology of granulomas explains why sputum microscopy may miss paucibacillary disease and why molecular tests are crucial for early detection. The concept of latency highlights the importance of preventive therapy for at-risk populations, while the role of immune-mediated tissue damage provides rationale for adjunctive host-directed therapies aimed at reducing pathology. These insights collectively emphasize that TB is not only a bacterial infection but also an immunopathological condition shaped by the host–pathogen relationship. [79]

Clinical Manifestations of Tuberculosis

Tuberculosis (TB) is a multisystem disease with diverse clinical presentations that reflect the site of infection, the immune status of the host, and the bacillary burden. While pulmonary TB is the most common form, accounting for the majority of cases worldwide, extrapulmonary and disseminated TB contribute significantly to morbidity and mortality, particularly in immunocompromised populations. [80]

Pulmonary Tuberculosis

Pulmonary TB is the primary driver of transmission and represents the classical presentation of the

disease. Symptoms are often insidious, developing gradually over weeks to months. The cardinal features include persistent cough lasting more than two weeks, hemoptysis, chest pain, fever, night sweats, and weight loss. In advanced cases, cavitary lesions form within the upper lobes of the lungs, leading to productive cough with sputum that is highly infectious. Chronic inflammation and tissue destruction contribute to long-term respiratory impairment even after successful treatment, underscoring the need for early diagnosis. [81,82]

Extrapulmonary Tuberculosis

Extrapulmonary TB (EPTB) occurs when bacilli spread beyond the lungs via lymphatic or hematogenous dissemination. Common sites include lymph nodes (scrofula), pleura, bones and joints, genitourinary tract, and meninges. TB meningitis, in particular, is associated with high mortality and long-term neurological sequelae if not promptly treated. Clinical features vary depending on the affected organ, which often complicates diagnosis. For instance, spinal TB (Pott's disease) may present with chronic back pain and risk of spinal deformity, while renal TB can mimic chronic urinary tract infection. In many regions, EPTB represents up to 20–30% of cases, with higher proportions among children and people living with HIV. [83,84]

Disseminated and Miliary Tuberculosis

Disseminated TB occurs when Mtb spreads widely through the bloodstream, leading to involvement of multiple organs. Miliary TB, characterized by a millet seed–like pattern of nodules on chest radiographs, is a classic but late manifestation of disseminated infection. Clinical signs include prolonged fever, hepatosplenomegaly, pancytopenia, and constitutional symptoms. Miliary TB is particularly common in infants, elderly individuals, and immunocompromised patients, where delayed diagnosis contributes to high fatality rates. [85]

TB in Special Populations

Certain groups are at higher risk for severe or atypical TB presentations. In children, disease progression is often more rapid due to immature immune responses, leading to higher rates of disseminated and meningeal TB. In the elderly, comorbidities and immunosenescence contribute to atypical or paucibacillary forms that may be misdiagnosed as other respiratory diseases. Among people living with HIV, TB may present without classical pulmonary features, instead manifesting as extrapulmonary or disseminated disease. Diabetes mellitus is also a recognized risk factor, associated with higher bacillary loads and worse outcomes. These variations highlight the need for tailored diagnostic and management strategies. [86,87]

Clinical Relevance

The wide clinical spectrum of TB poses significant diagnostic challenges, especially in resource-limited settings where confirmatory testing is often delayed. Overlapping symptoms with other respiratory infections, including COVID-19, further complicate recognition. Understanding the heterogeneity of TB presentations is critical for clinicians to avoid missed diagnoses, initiate early treatment, and reduce transmission. Furthermore, awareness of TB manifestations in vulnerable populations ensures that high-risk cases are not overlooked. [88]

Treatment of Tuberculosis

Effective treatment of tuberculosis is fundamental to reducing morbidity, mortality, and transmission. Therapeutic strategies are guided by drug-susceptibility patterns, patient comorbidities, and programmatic capacity.

Drug-susceptible tuberculosis (DS-TB):

The standard WHO-recommended regimen consists of a 6-month course of combination chemotherapy. This includes an intensive phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for two months, followed by a continuation phase of INH and RIF for four months [89]. This regimen achieves high cure rates when adherence is maintained, yet treatment completion remains a challenge in many settings. Directly observed therapy (DOT) or digital adherence technologies are frequently employed to minimize the risk of treatment interruption and subsequent drug

resistance [90].

Drug-resistant tuberculosis (DR-TB):

The emergence of multidrug-resistant TB (MDR-TB), defined by resistance to INH and RIF, has significantly complicated treatment efforts. Historically, regimens extended up to 20 months and relied heavily on injectable agents with substantial toxicity. Contemporary WHO guidelines now recommend all-oral regimens, incorporating bedaquiline, linezolid, and fluoroquinolones, with additional agents such as clofazimine or cycloserine [91]. Shorter regimens of 9–12 months may be utilized in carefully selected patients, though success rates remain variable. Despite these advances, global MDR-TB treatment success hovers around 60%, underscoring ongoing challenges related to drug toxicity, pill burden, and health system constraints [92,93].

Latent tuberculosis infection (LTBI):

Management of LTBI is a cornerstone of TB prevention. Treatment options include daily INH for 6–9 months, daily rifampicin for 4 months, or a 12-week once-weekly regimen of INH and rifapentine [94]. These regimens are particularly important for individuals at elevated risk of progression, such as those living with HIV, recent contacts of active TB cases, and patients with immunosuppressive conditions. Scaling access to LTBI treatment remains essential for advancing TB elimination goals.

Future directions:

Despite substantial progress, TB treatment continues to be hindered by drug toxicity, lengthy duration, and patient non-adherence. Research into host-directed therapies, therapeutic vaccines, and novel antimicrobials—including pretomanid-containing regimens—offers promise for shorter, safer, and more effective treatment strategies [95]. Expanding access to these innovations, particularly in high-burden countries, is critical to achieving global TB control targets.

Conclusion

Tuberculosis continues to represent one of the most significant infectious disease challenges worldwide. Despite being both preventable and curable, it remains a leading cause of morbidity and mortality, particularly in low- and middle-income countries. Advances in diagnostics, therapeutics, and preventive strategies have substantially improved patient outcomes; however, persistent gaps in access, adherence, and health system capacity limit their impact. The rise of drug-resistant forms of TB, the intersection with HIV, and disruptions caused by global health crises such as COVID-19 further underscore the fragility of current control efforts.

Sustained progress requires a multipronged approach: strengthening early case detection through innovative diagnostics, expanding access to shorter and less toxic treatment regimens, scaling preventive therapy in high-risk groups, and investing in novel interventions, including vaccines and host-directed therapies. Equally important is the reinforcement of health systems and global collaboration to ensure equity in TB care delivery.

Ultimately, eliminating tuberculosis will demand not only scientific innovation but also political commitment, sustained funding, and integrated public health strategies. With coordinated efforts, the global goal of ending TB as a public health threat can transition from aspiration to attainable reality.

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