Clinical Spectrum of Tuberculosis: From Latent Infection to Drug-Resistant Disease

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***Abstract*—Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis that spans a broad clinical spectrum from asymptomatic latent infection to severe, disseminated, and drug-resistant disease. Contemporary frameworks now view TB as a continuum that includes infection, incipient disease, subclinical TB, clinical disease, and post-TB lung disease. This paper reviews the clinical, radiological, and epidemiological spectrum of TB across pulmonary and extrapulmonary disease, with emphasis on the impact of immunocompromise and the growing burden of multidrug-resistant and extensively drug-resistant TB. Special focus is given to Indian programmatic data and recent consensus frameworks that shape diagnosis, risk stratification, treatment, and public health control.**

***Index Terms*—drug-resistant TB, extrapulmonary tuberculosis, India, latent infection, pulmonary tuberculosis, subclinical TB**

I. INTRODUCTION

Tuberculosis remains one of the world's leading infectious causes of death despite the availability of effective diagnostics and curative therapy. The 2024 WHO Global Tuberculosis Report indicates that TB has returned to being the leading infectious killer globally, surpassing COVID-19 and causing several million new cases and deaths annually. India carries the largest absolute burden, with hundreds of thousands of TB-related deaths and a high incidence of both drug-susceptible and drug-resistant disease, making a nuanced understanding of its clinical spectrum particularly relevant in this context.[3][4][15][2]

Historically, TB was described simplistically as either "latent" (infection without symptoms) or "active" (symptomatic disease), but clinical practice and pathogenesis research show a much more complex continuum. Patients may harbor metabolically active bacilli without symptoms or radiographic abnormalities, develop radiological lesions without overt symptoms, or present with classic constitutional and respiratory manifestations, while some survivors are left with chronic post-TB lung disease. Parallel to this biological continuum, TB can involve virtually any organ, creating a wide extrapulmonary spectrum that often poses diagnostic challenges and contributes significantly to morbidity.[7][9][10][5][12][1][6][2]

The aim of this paper is to synthesize current evidence on the clinical spectrum of TB across pulmonary, extrapulmonary, and drug-resistant forms, highlighting how emerging frameworks, epidemiological trends, and host factors shape this spectrum. Special emphasis is placed on data from India and on recent conceptual advances such as the 2024 Lancet framework defining early TB and subclinical disease states.[4][1][6][2] [^3]

II. PATHOGENESIS AND NATURAL HISTORY OF TUBERCULOSIS

TB transmission occurs predominantly via inhalation of droplet nuclei containing M. tuberculosis expelled by individuals with pulmonary or laryngeal disease. Following deposition in the alveoli, bacilli are phagocytosed by alveolar macrophages, initiating a complex immune response that may lead to clearance, latent infection, or progression to disease depending on bacillary load and host immunity.[5][2] [^3]

Latency is characterized by immunological containment of bacilli within granulomas, with no clinical symptoms and no evidence of disease on imaging, although immunodiagnostic tests such as tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) indicate infection. Approximately 5–10% of immunocompetent individuals with latent infection will develop active TB over their lifetime,

with higher risks in the first two to five years post-infection and in the presence of risk factors such as HIV, diabetes, malnutrition, and smoking.[1][2][3][5]
TB pathogenesis also underlies extrapulmonary manifestations: hematogenous or lymphatic dissemination during primary infection or reactivation can seed cervical lymph nodes, pleura, spine, meninges, abdominal organs, and genitourinary tract, giving rise to the diverse EPTB spectrum. This dissemination may occur early in infection, particularly in young children and immunocompromised hosts, or later as a consequence of reactivation of latent foci.[9][10][2][5]

III. CONCEPTUAL FRAMEWORKS FOR THE TB SPECTRUM

Recent work has sought to replace the binary latent-versus-active paradigm with a multistate model reflecting the continuum from infection to disease. A 2024 Lancet consensus framework, derived through Delphi methodology, proposes five dimensions that translate into four disease states: M. tuberculosis infection, subclinical TB, clinical TB, and post-TB lung disease.[6][5] [^1]
In this framework, infection (often termed latent TB infection) represents immunological evidence of M. tuberculosis without symptoms or radiographic abnormalities and no recognized disease state. Subclinical TB is defined as microbiologically confirmed TB in the absence of symptoms but with radiological or other pathological evidence of disease, and may be infectious or non-infectious depending on bacillary burden and site. Clinical TB denotes symptomatic disease with macroscopic pathology and usually higher infectiousness, encompassing classic pulmonary and extrapulmonary presentations. Post-TB lung disease refers to chronic structural and functional lung impairment following treated TB, such as bronchiectasis, cavitation, or airflow limitation, which contributes to long-term morbidity and requires follow-up care.[14][2][5][6]
Importantly, the framework emphasizes that subclinical TB may constitute 50–60% of community TB burden, implying that a substantial fraction of transmission and disease progression occurs before symptom onset. This has major implications for screening strategies, contact investigation, and the design of diagnostics capable of detecting early disease stages.[2][14] [^6]

IV. GLOBAL AND INDIAN EPIDEMIOLOGY UNDERPINNING THE SPECTRUM

Worldwide, TB remains highly prevalent, with millions of incident cases annually and disproportionate burdens in low- and middle-income countries. The 2024 WHO Global Tuberculosis Report describes TB as the leading infectious disease killer in 2023, underscoring ongoing gaps in detection and treatment coverage.[4][2]
India contributes the largest share of global TB incidence and mortality, with national program data documenting high case notification rates, persistent transmission, and rising attention to drug-resistant forms. As per national epidemiology resources, an estimated hundreds of thousands of TB-related deaths occurred in India in 2023, translating to dozens of deaths every hour and significant socio-economic impact.[15][3][^4]
The proportion of extrapulmonary TB has been increasing within India's overall TB burden, rising from approximately 16–18% of notified cases in 2017–2018 to around 24% by 2022 in some programmatic datasets. Site-specific studies from tertiary centers report that EPTB can account for more than 40% of all TB cases, with pleural and lymph node disease predominating but substantial frequencies of spinal, abdominal, and CNS TB. In parallel, national surveys indicate a substantial burden of MDR and XDR TB, further altering the clinical spectrum and complicating programmatic management.[8][10][11][12][7][15]

V. CLINICAL SPECTRUM OF PULMONARY TB

Pulmonary TB (PTB) remains the most common and epidemiologically important form because it drives airborne transmission. Classic symptoms include chronic cough lasting more than two weeks, hemoptysis, fever, night sweats, weight loss, and fatigue, although early disease and subclinical forms may be minimally symptomatic or asymptomatic.[3][5][1][2]
Radiographically, PTB may present with upper lobe infiltrates, cavitation, nodular lesions, or miliary patterns depending on stage and host factors. Chest

radiography remains a key screening tool, while computed tomography (CT) can detect subtle lesions and complications such as bronchiectasis, endobronchial disease, and small cavities. Incidentally detected radiological abnormalities suggestive of TB are increasingly reported, especially in high-burden settings and among patients undergoing imaging for other reasons, highlighting the importance of radiologist awareness of the TB spectrum.[10][2]

Spectrum manifestations in PTB include minimal lesions without symptoms, classic cavitary disease, extensive bilateral involvement, and miliary TB characterized by diffuse micronodular opacities from hematogenous spread. Clinical severity can range from mild cough and low-grade fever to severe respiratory failure in disseminated disease or acute respiratory distress syndrome, especially in immunocompromised patients.[10][5] [^2]

VI. CLINICAL SPECTRUM OF EXTRAPULMONARY TB

Extrapulmonary TB involves any site outside the lungs, including lymph nodes, pleura, skeletal system, CNS, abdomen, and genitourinary tract. Reviews and programmatic data suggest that EPTB accounts for approximately 15–25% of all TB cases globally, with higher proportions in HIV-infected patients, children, and some high-income settings.[16][9][2][10]

In India and other high-burden countries, hospital-based and registry studies show that lymph node and pleural TB are the most frequent EPTB forms, followed by spinal and abdominal disease. A retrospective study from Tamil Nadu reported that among 81 EPTB patients, cervical lymph node TB accounted for about one-third of cases and pleural effusion for nearly another third, with spinal, abdominal, and CNS TB comprising smaller but clinically significant proportions. Similar patterns are described in other Indian centers, where lymph node and spine involvement together exceed 60% of EPTB cases.[12][7] [^10]

Lymph Node Tuberculosis

Lymph node TB, often presenting as painless cervical or supraclavicular lymphadenopathy (scrofula), is among the commonest forms of EPTB. Nodes may be matted, fluctuant, or sinus-forming, and systemic symptoms may be mild or absent, particularly in early stages. Fine-needle aspiration cytology (FNAC) or biopsy with histology and microbiological testing aids diagnosis, and treatment outcomes are generally favorable with standard regimens, as reflected in retrospective Indian cohorts showing high cure rates among those completing therapy.[7][9][12][2] [^10]

Pleural Tuberculosis

Pleural TB typically presents with unilateral pleural effusion causing pleuritic chest pain, dyspnea, and fever, but may also manifest as chronic empyema or thickening. Pleural fluid is usually exudative and lymphocyte-predominant with elevated adenosine deaminase (ADA), and diagnosis may be supported by histology from pleural biopsy or molecular tests. Studies from Indian DOTS centers and tertiary hospitals consistently identify pleural TB as a leading EPTB manifestation, though outcomes can vary depending on comorbidities and timeliness of treatment.[9][12][16][7][2][10]

Skeletal and Spinal Tuberculosis

Skeletal TB, particularly Pott's disease of the spine, represents another important component of the EPTB spectrum, often presenting with chronic back pain, localized tenderness, deformity, or neurological deficits. Children show relatively higher rates of skeletal involvement compared with adults, and delay in diagnosis can result in irreversible spinal damage and paraplegia. Radiography, CT, and magnetic resonance imaging (MRI) are critical for assessing vertebral destruction, epidural collections, and spinal cord compression, while microbiological confirmation is sought through biopsy where feasible.[12][16][2][9] [^10]

Central Nervous System Tuberculosis

CNS TB includes tuberculous meningitis, intracranial tuberculomas, and spinal arachnoiditis, typically arising from hematogenous spread. Clinical manifestations range from subacute fever and headache to altered sensorium, seizures, and focal neurological signs, often with high mortality and risk of long-term sequelae despite treatment. Early recognition using cerebrospinal fluid analysis, neuroimaging, and rapid molecular tests is essential, as delayed therapy is strongly associated with poor outcomes in both adults and children.[16][2][9][10]

Abdominal and Genitourinary Tuberculosis

Abdominal TB may involve the peritoneum, intestinal tract, lymph nodes, or solid organs and can present with ascites, abdominal pain, weight loss, or bowel obstruction, frequently mimicking malignancy or inflammatory bowel disease. Genitourinary TB, including renal, ureteric, bladder, and genital tract involvement, may present with sterile pyuria, hematuria, infertility, or obstructive uropathy and may remain asymptomatic for prolonged periods. Both entities demand high clinical suspicion and often require a combination of imaging, endoscopy, histopathology, and microbiological testing for definitive diagnosis.[2][9][10][16]

VII. TB IN IMMUNOCOMPROMISED AND VULNERABLE POPULATIONS

Host immunity profoundly influences the TB spectrum, with immunocompromised individuals showing atypical presentations, higher risk of extrapulmonary and disseminated disease, and worse outcomes. HIV infection is the strongest risk factor for progression from infection to disease, and people living with HIV (PLHIV) have a higher prevalence of EPTB, smear-negative PTB, and miliary TB.[5][9][10][2]

Guidelines from WHO and national programs emphasize intensified case finding among PLHIV, including routine TB symptom screening, chest radiography, and use of rapid molecular diagnostics like Xpert MTB/RIF. TB is a leading cause of death in PLHIV globally, and integrated TB–HIV services, including cotrimoxazole prophylaxis, antiretroviral therapy, and isoniazid preventive treatment, are crucial to reduce incidence and mortality.[3][4][5][2]

Other vulnerable groups include children, older adults, people with diabetes, those on immunosuppressive therapies (e.g., TNF-alpha inhibitors, corticosteroids), and individuals in congregate settings such as prisons and slums. Pediatric TB often manifests as intrathoracic lymph node disease, miliary TB, or severe forms like meningitis, reflecting a higher propensity for dissemination. Elderly patients may present with non-specific symptoms and higher rates of comorbidity, complicating diagnosis and management and influencing the clinical spectrum toward atypical radiographic patterns and higher mortality.[11][9][10][5][2][3]

VIII. DRUG-RESISTANT TB AND ITS IMPACT ON THE SPECTRUM

The emergence and spread of drug-resistant TB, particularly MDR TB (resistance to at least isoniazid and rifampicin) and XDR TB (MDR plus resistance to fluoroquinolones and second-line injectable agents), have profoundly affected the TB spectrum. National surveys estimate that India alone accounts for a large share of global MDR/rifampicin-resistant TB, with tens of thousands of incident cases annually.[13][8][11][15]

A first national anti-TB drug resistance survey in India estimated substantial proportions of MDR and rifampicin-resistant cases among both new and previously treated patients, with XDR TB representing around 6% of MDR TB cases. Systematic reviews indicate that globally the pooled proportion of XDR TB among MDR TB patients is approximately 9%, with some of the highest proportions reported from India and other high-burden countries.[11][13] [^15]

Clinically, MDR/XDR TB often presents similarly to drug-susceptible TB but is characterized by prior treatment exposure, persistent or recurrent symptoms, and radiological features such as bilateral cavitary disease and extensive fibrosis. Treatment is longer, more toxic, and less effective, with lower cure rates and higher mortality, thereby extending the duration of infectiousness and amplifying transmission within communities.[8][13][15][11]

A retrospective analysis from Kerala, India, reported 128 notified DR-TB cases over five years, with a mix of monoresistant, polyresistant, MDR, and pre-XDR/XDR patterns and substantial proportions of unfavorable outcomes. Factors associated with poor outcomes included delayed diagnosis, comorbidities, and loss to follow-up, highlighting health-system determinants that shape the clinical and epidemiological spectrum of DR-TB.[13][8]

IX. DIAGNOSTIC APPROACHES ACROSS THE SPECTRUM

The diversity of TB presentations requires a multimodal diagnostic strategy combining clinical evaluation, imaging, microbiology, and molecular testing. For pulmonary disease, sputum smear microscopy remains widely used but has limited sensitivity, especially in HIV-positive and subclinical

cases, whereas rapid molecular tests such as Xpert MTB/RIF and line probe assays significantly improve detection and provide early drug resistance information.[5][2]

Culture on solid or liquid media remains the reference standard for confirmation and drug susceptibility testing, though it is time-consuming and requires laboratory capacity. Radiological tools, including chest X-ray and CT, are essential for screening, staging, and follow-up, particularly for early or incidental lesions suggestive of subclinical disease and for complex EPTB sites.[10][2] [^5]

In extrapulmonary TB, diagnosis often hinges on obtaining appropriate specimens through invasive procedures such as lymph node aspiration, pleural biopsy, bone and spine biopsy, or cerebrospinal fluid sampling, combined with histopathology, culture, and molecular tests. Biomarkers like ADA in pleural and peritoneal fluid, alongside imaging modalities (ultrasound, CT, MRI), support diagnosis where microbiological yield is low but clinical suspicion remains high.[9][16] [^2]

Latent infection is detected using TST or IGRAs, particularly in high-risk groups such as contacts of infectious cases, PLHIV, and patients initiating immunosuppressive therapy. Emerging research on minimal and subclinical TB explores novel biomarkers and imaging signatures that may help stratify risk and guide preventive therapy, reflecting the shift toward an expanded understanding of the spectrum.[14][6][2][3]

X. TREATMENT, OUTCOMES, AND POST-TB SEQUELAE

Standard treatment for drug-susceptible TB typically consists of a multidrug regimen, historically based on isoniazid, rifampicin, pyrazinamide, and ethambutol for an initial intensive phase followed by continuation with fewer drugs. Treatment durations for pulmonary and many extrapulmonary forms are generally six months, although some sites such as CNS and skeletal TB may require extended therapy.[16][2][^9]

Recent WHO guidelines have endorsed shorter, all-oral regimens for MDR/RR-TB using combinations of bedaquiline, linezolid, levofloxacin or moxifloxacin, and other agents, aiming to improve adherence and outcomes compared with older, injectable-based regimens. Nevertheless, MDR/XDR TB treatment remains complex, with significant adverse events and lower success rates than drug-susceptible disease, and outcomes are strongly influenced by timely diagnosis, adherence support, and management of comorbidities.[15][8][11][13]

EPTB treatment generally follows pulmonary regimens but may need tailoring to site-specific considerations such as the need for adjunctive corticosteroids in meningitis or pericarditis and for surgical intervention in spinal instability, large abscesses, or obstructive lesions. Programmatic studies show high cure or completion rates in lymph node and pleural TB when diagnosis is prompt and adherence is supported, whereas spinal, abdominal, and CNS TB often have poorer outcomes and higher rates of disability or death.[7][12][2][9][10][16]

Post-TB lung disease is increasingly recognized as a distinct state on the spectrum, encompassing persistent airflow limitation, bronchiectasis, residual cavitation, and chronic respiratory symptoms following microbiological cure. This condition contributes to long-term morbidity and reduced quality of life and may predispose to recurrent infections and non-communicable respiratory diseases, calling for structured follow-up and integration of TB and chronic respiratory care.[6][2] [^5]

XI. IMPLICATIONS FOR TB CONTROL AND ELIMINATION

Recognition of the full TB spectrum has important implications for public health strategies aimed at elimination. The high prevalence of subclinical TB suggests that reliance on symptom-based screening alone will miss a large proportion of infectious individuals, underscoring the need for radiographic or biomarker-based screening in high-risk populations and settings.[14][6][2][3]

The growing share of EPTB in India and elsewhere highlights the need to strengthen diagnostic capacity beyond sputum-based tools, including wider availability of imaging, pathology, and molecular testing for non-pulmonary specimens. Management of TB in immunocompromised and vulnerable populations requires integrated services, social support, and targeted preventive therapy to interrupt progression from infection to disease.[7][2][9][3][10][5] [^16]

Escalating MDR/XDR TB burdens necessitate robust drug-resistance surveillance, rapid DST for all diagnosed cases, access to newer all-oral regimens, and adherence support to prevent amplification of resistance. Addressing social determinants such as poverty, malnutrition, overcrowding, and stigma remains essential, as these factors shape both the epidemiological and clinical spectrum of TB in high-burden regions.[8][4][11][15][^3]

XII. CONCLUSION

The clinical spectrum of tuberculosis extends far beyond the traditional dichotomy of latent versus active disease, encompassing a continuum from infection through incipient and subclinical states to overt pulmonary and extrapulmonary disease and post-TB sequelae. This spectrum is shaped by mycobacterial factors, host immunity, comorbid conditions, and socio-economic determinants and is increasingly modulated by the rise of drug-resistant strains.[1][4][13][6][8][2][3][5]

A nuanced understanding of this spectrum is crucial for clinicians managing diverse TB presentations, for researchers developing diagnostics and therapeutics targeting early and drug-resistant disease, and for policy makers designing elimination strategies that go beyond symptomatic case finding. Future research priorities include better characterization of minimal and subclinical TB, improved tools for EPTB diagnosis, optimization of shorter regimens for both drug-susceptible and drug-resistant disease, and integrated models of care that address post-TB lung disease and social determinants.[4][11][6][2][^14]

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