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Tuberculosis: An Interdisciplinary Overview For Laboratory, Nursing, And Epidemiology Practice

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Abstract:

Background: Tuberculosis (TB) remains a leading infectious cause of morbidity and mortality worldwide, characterized by complex diagnostic, therapeutic, and preventive challenges. Despite being preventable and curable, TB persists due to biological, social, and systemic factors.

Aim: This review aims to provide an interdisciplinary synthesis of TB's etiology, epidemiology, pathophysiology, diagnostic strategies, treatment approaches, and public health implications for laboratory, nursing, and epidemiology professionals.

Methods: A comprehensive literature review was conducted using WHO global reports, CDC guidelines, and peer-reviewed studies to integrate historical and contemporary perspectives on TB biology, clinical management, and control strategies.

Results: TB is caused primarily by Mycobacterium tuberculosis, an intracellular pathogen with slow growth and latency potential. Approximately 25% of the global population harbors latent infection, with 10.6 million active cases reported in 2022. Diagnostic challenges persist due to nonspecific symptoms, low bacillary burden, and resource limitations. Advances such as nucleic acid amplification tests (NAATs) and interferon-gamma release assays (IGRAs) have improved detection, yet access remains inequitable. Treatment requires prolonged multidrug regimens; recent innovations include shorter preventive therapy and new drugs for resistant TB. Drug resistance and TB–HIV coinfection remain critical threats.

Conclusion: Effective TB control demands integrated strategies combining rapid diagnostics, patient-centered care, and robust public health infrastructure. Interprofessional collaboration is essential to achieve WHO's goal of 90% incidence reduction by 2035.

Keywords: Tuberculosis, Mycobacterium tuberculosis, latent infection, diagnostics, drug resistance, public health, nursing, epidemiology.

Introduction:

Tuberculosis remains a major infectious disease with persistent clinical and public health impact. It affects millions despite decades of scientific progress and policy action. The disease includes a wide spectrum. Latent infection causes no symptoms. Active disease can involve multiple organs. Diagnosis is often delayed. Treatment requires long regimens. Prevention depends on sustained individual and population level action. Historically TB has caused more deaths than any other infectious disease. This fact reflects its deep epidemiologic burden and its ability to persist despite advances in medicine and health systems [1], [Global tuberculosis report 2024. Geneva: World Health Organization]. Although TB is preventable in principle, real world control is limited by social determinants, unequal healthcare access, and variable effectiveness of interventions. This gap between theoretical prevention and ongoing transmission illustrates the interaction between biological pathogens and structural inequities. Mycobacterium tuberculosis has coexisted with humans for thousands of years. It grows slowly and establishes prolonged host–pathogen interactions. The organism can persist in a latent state for years. It evades immune clearance and exploits immune weakness caused by malnutrition, comorbid disease, immunosuppression, or overcrowding. As a result, TB remains relevant in urban centers, rural regions, and high income countries among vulnerable populations. Global policy reflects recognition of TB as preventable. The World Health Organization aims to reduce TB incidence by 90 percent between 2015 and 2035. This target highlights both urgency and the large gap in detection, treatment completion, and transmission control that must be closed [1][2][3].

Scientific understanding of TB developed over a long period. Koch identified the causative bacterium in 1882. This discovery shifted TB from a wasting illness to a defined microbial disease [2]. Progress remained slow because of the organism's biology. More than a century later genome sequencing of M tuberculosis enabled insight into virulence, strain variation, and drug resistance [2]. These advances improved surveillance and management but did not eliminate diagnostic difficulty. Undetected cases sustain transmission. Delayed diagnosis worsens outcomes and increases spread. Diagnostic strategies include immune based tests, microbiologic methods, and clinical or radiologic assessment. The Mantoux tuberculin skin test has been used since 1909 and remains widespread [3]. It is accessible but indirect since it measures immune response rather than detecting the organism. Interpretation depends on immune status and exposure risk. Interferon gamma release assays introduced in 2014 aimed to improve specificity and convenience [3]. Like the skin test they depend on host immunity. Both tests require careful interpretation alongside epidemiologic and clinical context [1][2][3]. Direct detection of M tuberculosis presents major laboratory challenges. The organism grows slowly and may be present in low numbers. Detection is difficult in poor quality samples and in extrapulmonary disease [4]. Culture delays confirmation and susceptibility testing. Specimen collection is often challenging for patients and nursing staff. These factors complicate surveillance and burden estimation. Molecular diagnostics such as nucleic acid amplification tests enable faster identification [4]. Earlier confirmation supports timely treatment and infection control. Access remains uneven due to resource and infrastructure constraints. Integration of these tools into local algorithms continues to evolve [1][2][3][4].

Diagnostics continue to advance with new tools aimed at improving accuracy and feasibility [5]. Effective tests must be scalable and affordable in high burden settings and precise in low burden contexts. Improved diagnostics reduce untreated infectious periods and support public health goals. Implementation requires training and quality systems across professions [5]. Treatment also remains challenging. TB therapy requires multiple drugs over long durations. Many core drugs date to the mid twentieth century. Recently two new anti TB agents were approved after more than 40 years [6]. These drugs address resistance but do not remove challenges related to adherence, toxicity, and health system barriers [5][6].

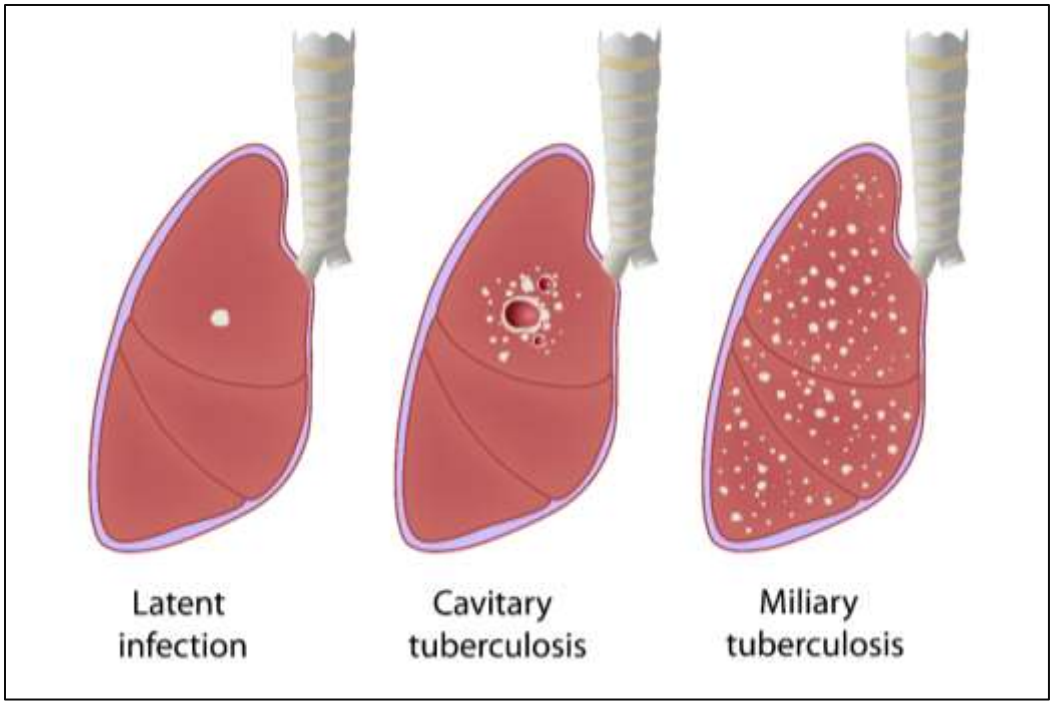

Fig. 1: Different Types of Tuberculosis.

TB treatment varies by disease stage, site of infection, and patient factors. The difference between latent infection and active disease is critical. Active TB treatment targets eradication of replicating organisms, relapse prevention, and transmission reduction. Latent TB treatment targets dormant organisms to prevent future disease. Regimen choice also depends on pulmonary versus extrapulmonary involvement, immune status, and age. These factors influence severity, dissemination risk, and drug tolerance. Comorbidities and concurrent medications complicate care due to frequent drug interactions. Toxicity risk requires structured monitoring and may force regimen changes. Effective treatment therefore depends on coordinated clinical judgment, laboratory follow up, and patient support to sustain adherence. Drug resistance represents a major threat to TB control. Resistant TB requires complex regimens that often rely on limited clinical trial evidence. Clinicians must individualize therapy while balancing incomplete data and patient safety. Resistant disease increases treatment duration, adverse effects, and monitoring demands. Even drug susceptible TB poses challenges. Long treatment courses reduce adherence over time. Side effects accumulate. Social and economic pressures disrupt follow up. These barriers intensify in patients facing housing instability, income insecurity, or transport limits. Treatment success depends on integrated systems that support adherence, manage toxicity, and maintain continuity of care [5][6][7].

Shorter regimens for latent TB represent an important advance. They reduce adverse events and improve completion rates [7]. Higher completion lowers future incidence in high risk groups. Shorter regimens also simplify follow up and reduce cumulative toxicity. Implementation still requires structured identification, counseling, monitoring, and documentation. Nurses play a central role in education, adherence assessment, and coordination. Laboratory teams support baseline and follow up safety testing. Epidemiologists identify high risk populations and evaluate program impact. Pharmacologic progress alone is insufficient without operational support. Prevention remains difficult due to social and structural factors. Poverty, crowding, and weak public health systems sustain transmission. Nonspecific symptoms delay care seeking. Barriers include stigma, limited diagnostics, and indirect costs. Long treatment further complicates completion. Prevention therefore depends on health system strengthening, surveillance, contact tracing, education, and community support [7]. High burden regions often lack diagnostic and follow up capacity. Low burden regions face low clinical suspicion and delayed diagnosis. TB control is both a biomedical and

implementation challenge. Effective control requires coordinated laboratory services, nursing care, clinical management, and epidemiologic surveillance aligned with equitable health system investment [1][2][3][4][5][6][7].

Etiology

Tuberculosis originates from a group of closely related organisms known as the Mycobacterium tuberculosis complex. This complex includes several species with shared genetic structure and similar disease potential in humans and animals. Mycobacterium tuberculosis causes most human disease worldwide, yet other members such as M bovis, M africanum, and M canetii also infect humans and shape regional epidemiology. Their distribution depends on geography, animal contact, and public health systems. Recognizing the full complex is essential for understanding zoonotic transmission, surveillance design, and TB ecology [8][9]. MTBC organisms share key microbiologic traits. They are aerobic, nonmotile, and non–spore forming bacilli. Their defining feature is a lipid rich cell wall. This structure produces acid fast staining and directly influences pathogenic behavior. The lipid envelope limits penetration of immune factors and antimicrobial agents. It supports intracellular survival and persistence within host tissues. These properties complicate eradication and reflect a survival strategy under hostile immune conditions [8].

Slow growth is a central etiologic feature. M tuberculosis divides roughly every 20 hours. In the laboratory this requires culture incubation of three to eight weeks. This delay affects diagnosis, drug susceptibility testing, and transmission control. Untreated individuals may remain infectious while confirmation is pending. Slow replication also explains the need for prolonged antimicrobial therapy. In settings without rapid molecular diagnostics, this feature remains a major cause of delayed care. Human beings serve as the only confirmed natural reservoir for M tuberculosis. Sustained human to human transmission drives the global burden. This reality supports prevention strategies focused on early detection, treatment, and contact tracing. Other MTBC members such as M bovis involve animal reservoirs and zoonotic pathways. These cases link TB control to veterinary health, food safety, and occupational risk management [8][9]. Genetic variation within MTBC influences disease behavior. Distinct lineages affect transmission patterns and possibly virulence. Molecular epidemiology helps define outbreaks and guide interventions. MTBC organisms persist intracellularly and can enter dormancy. This capacity underlies latent TB infection and future reactivation. Mechanisms of dormancy remain unclear and limit prediction and targeted prevention. TB etiology therefore reflects a dynamic interaction between pathogen persistence and host immunity rather than simple exposure [2][8][9].

Epidemiology

Tuberculosis epidemiology is defined by the dominance of latent infection overactive disease. After infection with Mycobacterium tuberculosis, about 90 percent of individuals develop latent infection without symptoms. This group forms a large reservoir that sustains long term population risk. Around 5 percent progress to active disease within two years and another 5 percent reactivate later in life. These patterns show that TB is a chronic infectious process rather than an acute illness. Progression risk varies widely and depends on host vulnerability and environment. Immunocompromised states drive risk because cell mediated immunity is essential for control. Major factors include HIV infection older age immunosuppressive therapy transplantation corticosteroid exposure chemotherapy TNF antagonists malnutrition and diabetes. Tobacco use and harmful alcohol consumption also increased risk through physiologic and social pathways. These determinants guide targeted screening and preventive treatment strategies [9][10]. Global surveillance data highlight TB persistence. In 2022 TB caused 1.3 million deaths worldwide which reflects a modest decline from prior years but still represents a major cause of infectious mortality [WHO. World TB Report 2023.]. TB remains the leading cause of death among people living with HIV and accounted for 167,000 deaths in this group in 2022. In the same year 7.5 million people were diagnosed with TB which is the highest number since systematic monitoring began. Diagnosed cases were concentrated in Southeast Asia Africa and the Western Pacific. These patterns reflect differences in health system capacity socioeconomic conditions and comorbidity prevalence. An estimated 10.6 million people

were living with active TB including men women and children. Pediatric cases are epidemiologically important because they indicate recent transmission and prevention gaps [10][11].

At the population level about 25 percent of the world's population is infected and 5 to 10 percent will develop active disease over a lifetime [WHO. World TB Report 2024.]. This dual burden of latent infection and active disease defines TB control challenges. Incidence reduction requires both interruption of transmission and prevention of reactivation. Laboratory services must support diagnosis and resistance detection. Clinical and nursing teams must sustain adherence and follow up for both active and preventive therapy. The United States illustrates risks in low incidence settings. In 2023 there were 9,615 new cases which equals 2.9 cases per 100,000 persons and a 16 percent increase from 2022 [10]. This rise followed decades of decline and occurred across age groups and states. Children aged 5 to 14 years showed a marked relative increase which signals recent transmission despite small absolute numbers [10]. People born outside the United States accounted for 76 percent of cases and about 85 percent resulted from reactivation of latent infection. HIV coinfection occurred in 5 percent of cases [10]. The COVID 19 pandemic disrupted TB control worldwide. Reduced access to care and diagnostics led to delayed detection and excess mortality. An estimated half million excess TB deaths occurred between 2020 and 2022 [11]. Drug resistant TB adds further complexity. Significant proportions of cases show isoniazid or rifampin resistance and MDR TB remains underdiagnosed and undertreated [12][13]. These realities confirm that TB epidemiology reflects sustained interaction between biology health systems and social conditions requiring continuous coordinated investment [11][12][13][14].

Pathophysiology

Tuberculosis (TB) pathophysiology reflects a prolonged, highly adaptive interaction between Mycobacterium tuberculosis (Mtb) and the human immune system. Unlike many respiratory pathogens that produce short-lived, self-limited disease in a large proportion of exposed individuals, Mtb is characterized by slow growth, intracellular persistence, and an exceptional ability to remain clinically silent for extended periods. The clinical course that follows exposure is neither uniform nor strictly deterministic. Instead, outcomes are shaped by the size of the inoculum, the duration and intensity of exposure, host immune competence, and a range of microbial and environmental variables. For laboratory, nursing, and epidemiology teams, understanding TB pathophysiology is essential because it explains why transmission can be efficient in certain settings, why diagnostic confirmation may be delayed, why treatment is prolonged, and why reinfection, reactivation, and dissemination occur under specific circumstances [13][14].

Transmission and initial establishment of infection

Mtb is transmitted most commonly through airborne droplet nuclei generated when a person with active pulmonary or laryngeal TB coughs, sneezes, speaks, or sings. These droplet nuclei can remain suspended in air for several hours, particularly in poorly ventilated indoor environments, and thus can be inhaled by susceptible individuals long after the infectious person has left the area. Transmission probability increases with prolonged exposure in enclosed spaces where droplet nuclei are present, reflecting the combined effect of inhalation dose and the persistence of aerosols in stagnant air. This is why TB outbreaks historically have been associated with congregate settings—households, shelters, correctional facilities, crowded wards, and other spaces where ventilation is limited and close contact is sustained. Although airborne spread is the dominant route, other acquisition pathways have been documented. Ingestion of contaminated milk can transmit mycobacteria, historically associated with M bovis and unpasteurized dairy; however, this route has become rare in many regions due to pasteurization and veterinary control measures. TB bacilli may rarely be introduced through contact with droplet nuclei or fomites in the presence of nonintact skin, but such mechanisms are exceptional and contribute minimally to population-level transmission. The dominance of airborne spread remains the primary reason that infection control measures emphasize ventilation, respiratory protection, and rapid identification and treatment of infectious cases. Not every inhalational exposure results in established infection. Droplet nuclei may deposit in the upper airway

mucosa, where clearance mechanisms and local immune defenses often prevent infection from taking hold. Effective infection establishment is more likely when bacilli reach the alveoli, where the pathophysiologic cascade typically begins. At this point, the outcome is contingent on a complex set of virulence factors and host immune responses. The bacillus may be eliminated rapidly, may persist without causing clinical disease, or may progress to active disease. These outcomes are often described as discrete categories—clearance, latent infection, and active TB—but the modern understanding increasingly recognizes that this tripartite model oversimplifies a dynamic continuum. Contemporary immunologic insights suggest that the host–pathogen relationship can shift over time, with transitions between states influenced by changes in immune function, bacterial metabolic activity, and local tissue microenvironments.[14][15] Moreover, some elements of the classic pathophysiologic model have been questioned as immunology has advanced, emphasizing the need to view TB as a spectrum rather than a binary latent-versus-active phenomenon.[16]

Innate immune response and the central role of alveolar macrophages

Alveolar macrophages represent the first major cellular line of defense and are central to early immunomodulation. After deposition in the alveoli, bacilli are internalized by macrophages through phagocytosis. At this point, two broad outcomes are possible. In some cases, macrophages successfully kill the bacilli through antimicrobial mechanisms. In other cases, Mtb survives intracellularly and establishes primary infection. Intracellular survival is facilitated by Mtb's ability to resist degradation within phagolysosomes, to manipulate host cell signaling, and to adapt to nutrient-limited and oxidative environments. When survival occurs, bacilli replicate slowly within macrophages and can extend into adjacent lung parenchyma, initiating local inflammatory responses. The early phase of infection also involves migration of infected macrophages and antigen-presenting cells to regional lymphatic structures, particularly pulmonary lymph nodes. In these nodes, antigen presentation primes T lymphocytes—especially CD4+ T cells—leading to a coordinated adaptive immune response. The primed T cells then orchestrate recruitment of additional immune cells, including further T cells, B cells, monocytes, multinucleated giant cells, dendritic cells, and fibroblasts. This cellular recruitment contributes to the formation of a granuloma, a structured immune aggregate that develops around infected macrophages within lung tissue. Granuloma formation is central to TB pathophysiology because it represents the host's attempt to contain infection while simultaneously creating a microenvironment in which bacilli can persist. The immunologic mechanisms that govern granuloma formation and the life cycle of Mtb within granulomas remain incompletely defined and continue to be an area of intensive research.[17][18][19][15]

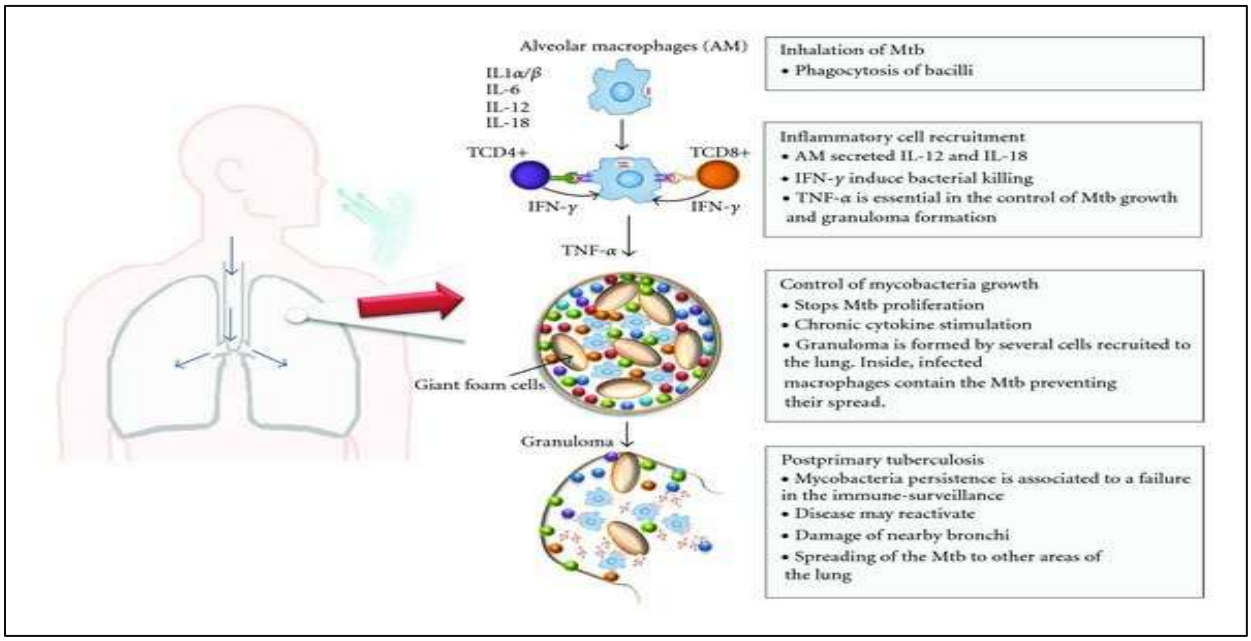

Fig. 2: Pathogenesis of Tuberculosis.

Granuloma evolution, Ghon focus, and Ranke complex

The earliest organized lesion in primary pulmonary TB is often described as a "Ghon focus," a parenchymal granuloma that forms at the site of initial infection. When the associated draining hilar or mediastinal lymph nodes are involved, the combination constitutes the primary complex. Over time, some of these lesions undergo calcification, and if sufficiently large, calcified lesions may be visible on a chest radiograph. When a calcified parenchymal focus is seen together with calcified regional lymph nodes, this radiographic finding is known as the "Ranke complex." While not all primary lesions calcify and not all calcifications represent TB, the concept is clinically useful because it illustrates that primary infection can leave enduring radiologic signatures even after clinical quiescence has been achieved. The evolution of primary lesions differs by host factors, particularly age and immune competence. In children, intrathoracic lymph nodes may enlarge substantially, causing airway compression or erosion into bronchi. This can produce significant respiratory compromise and contributes to the clinical complexity of pediatric TB. In immunocompromised adults and in children, the Ghon focus may progress to a form of pneumonia that is often localized in lower lung zones, where cavitation is less common than in adult reactivation disease. In young children, progressive primary TB can disseminate rapidly in a miliary pattern and may cause life-threatening TB meningitis, illustrating how the same pathogen can yield markedly different pathophysiologic trajectories depending on immune maturity and host susceptibility [17][18][19].

Latency, dissemination, and the spectrum of subclinical disease

In most immunocompetent adults, granulomas successfully contain bacilli, producing what is traditionally labeled latent TB infection. In this state, viable organisms persist, but clinical disease does not manifest. Yet even in immunocompetent hosts, containment is not absolute. Bacilli can escape local immunologic controls and disseminate lymphohematogenously, either within the lungs or to distant organs. Within the lung, dissemination often favors apical posterior segments. The reason for this predilection is not definitively established; hypotheses include higher regional oxygen tension that may favor Mtb metabolism, differences in lymphatic drainage that affect immune trafficking and bacillary clearance, and regional differences in pulmonary immune function. Regardless of mechanism, this anatomic pattern is a defining feature of adult and adolescent TB and has direct implications for radiologic evaluation and clinical suspicion. Extrapulmonary dissemination can involve virtually any organ system. The pleura, lymph nodes, kidneys, long bones, vertebrae, and meninges are among the organs most commonly associated with extrapulmonary TB.[20] After bacilli seed these sites, they may proliferate until cellular immunity is established locally, after which bacilli can become dormant. In immunocompetent people, this immunologic control is often established within approximately 3 to 8 weeks after infection. CD4+ and CD8+ T cells appear to play central roles in controlling bacillary replication and maintaining latency.[16] This temporal window—during which dissemination may occur before full adaptive containment is established—helps explain why early infection can seed multiple sites yet remain clinically silent, only to reactivate later when immune pressures change [16]. An important refinement to the classic latent-versus-active framework is the recognition that latent TB is not necessarily synonymous with complete bacterial dormancy. Individuals labeled as having latent TB may cycle between periods of dormancy and episodes of subclinical disease activity, in which bacilli replicate at low levels without producing overt symptoms. This concept is supported by surveillance findings in regions of high endemicity, where active case-finding reveals high prevalence of asymptomatic TB disease and where the boundary between infection and disease appears more fluid than previously assumed.[15][21][22] For epidemiologists, this has major implications: "latent TB" may include a subset of individuals who are closer to progression than traditional models suggest, altering the calculus of preventive therapy. For clinicians and nursing teams, it highlights why symptom screening alone may miss early disease, particularly in high-risk groups. For laboratories, it underscores the importance of sensitive diagnostic methods capable of detecting low-bacillary-burden disease [20][21][22].

Progression to active disease and the pathogenesis of cavitation

When innate and adaptive immunity fail to contain Mtb, active TB disease develops. Pathophysiologically, granulomas may undergo caseation necrosis, an immune-mediated process in which the center of the granuloma becomes necrotic and lipid-rich, producing the characteristic "caseous" material. Over time, the necrotic center may liquefy and erode into an airway. When this occurs, a pulmonary cavity can form. Cavitation is a pivotal event in TB pathophysiology because it transforms contained infection into a highly transmissible state. The cavity communicates with the bronchial tree, enabling bacilli to enter the airways, be coughed into the environment, and infect others.[23] Cavities also represent a distinctive microenvironment for bacillary proliferation and antimicrobial challenge. They often contain high concentrations of organisms, while their inner contents may be poorly vascularized, limiting immune cell access and reducing drug penetration. This combination can promote the emergence of drug resistance, as bacilli exposed to suboptimal drug concentrations in a high-burden compartment are more likely to select for resistant mutants. Clinically, cavitary disease is associated with greater infectiousness, more extensive tissue destruction, and often a higher risk of relapse if treatment is inadequate. Functionally, cavitated lung tissue no longer contributes effectively to gas exchange, and surrounding parenchyma may become fibrotic, leading to long-term respiratory impairment. Cavitation also increases the risk of secondary complications. Cavities can act as niches for opportunistic bacterial or fungal colonization. In addition, pulmonary blood vessels adjacent to cavitary lesions can erode, producing a "Rasmussen aneurysm"—a pseudoaneurysm of a pulmonary artery branch within or adjacent to a cavity—which can precipitate massive hemoptysis. Hemoptysis in TB thus ranges from minor blood-streaked sputum to life-threatening hemorrhage, reflecting the degree of vascular involvement. Importantly, not all granulomas cavitate; some involute and heal through immunologic mechanisms that remain incompletely characterized. Understanding why certain lesions heal while others cavitate remains an active research area and has implications for predicting disease severity and transmission risk. Epidemiologically, active TB develops in approximately 5% of recently infected individuals within the first two years after infection, with an additional 5% progressing later in life. This progression pattern reflects both early failure of immune containment and later reactivation from previously controlled foci. The balance between these mechanisms differs across populations, influenced by HIV prevalence, nutritional status, diabetes burden, and access to preventive therapy [22][23][24].

Clinical spectrum, asymptomatic disease, and age-related patterns

Active TB manifests along a broad clinical spectrum. At one end, individuals may be asymptomatic yet harbor microbiologically active disease; at the other end, individuals may be severely ill with extensive pulmonary destruction or disseminated extrapulmonary involvement. Disease manifestations depend on the organs affected. In adults and adolescents, the apical posterior lung segments are most frequently involved, consistent with the pathophysiologic predilection described earlier. In young children and in older adults, lower-lobe pneumonic patterns are more common, reflecting differences in immune function, airway anatomy, and the relative predominance of progressive primary disease. Constitutional symptoms are classically nonspecific and include cough, fever, weight loss, night sweats, and malaise. Because these symptoms overlap with many other respiratory and systemic illnesses, TB can be missed, particularly in low-incidence settings where clinical familiarity is limited. Asymptomatic TB disease is increasingly recognized, especially when active case-finding is performed in high-risk populations. Studies suggest that prevalence of asymptomatic active disease can be substantial when screening is proactive, supporting the view that symptom-based detection underestimates disease burden.[14][24] This has direct implications for public health strategies. In high-burden settings, relying on passive case detection—waiting for symptomatic individuals to present—may allow prolonged transmission from minimally symptomatic or asymptomatic infectious individuals. In low-burden settings, asymptomatic disease may still occur among high-risk groups such as recent contacts, individuals with HIV, or those undergoing immunosuppressive therapy, reinforcing the need for targeted screening. Endobronchial TB represents a distinct complication arising from the spread of organisms into the airway, typically from a pulmonary cavity, a pneumonic focus, or an adjacent infected lymph node. The pathophysiologic hallmark is inflammatory involvement of the

bronchial mucosa, which can produce ulcerations, granulation tissue, mucosal edema, and airway narrowing.[25] These changes can lead to persistent cough, wheezing, recurrent pneumonia due to obstruction, and long-term airway stenosis even after microbiologic cure. The development of airway narrowing emphasizes why early recognition and appropriate management are important: structural damage can persist even when the infection is eradicated [14][22][23][24][25].

Reactivation, reinfection, relapse, and epidemiologic interpretation

The most common mechanism of active TB in many settings is reactivation of a latent focus. Reactivation occurs when immunologic containment weakens and dormant or intermittently replicating bacilli resume active proliferation. Previously infected individuals are generally partially protected against exogenous reinfection, but reinfection remains possible, particularly in settings of high exposure intensity or in individuals with significant immunosuppression. Distinguishing relapse (endogenous reactivation due to failure to eradicate the original infection) from new exogenous reinfection is often challenging but has important therapeutic and epidemiologic implications.[26] Clinically, relapse may suggest inadequate prior therapy, poor adherence, or drug resistance, whereas reinfection may indicate ongoing transmission risk in the community or household. Epidemiologically, the distinction affects how programs interpret incidence and evaluate control measures. Molecular typing and genomic approaches can sometimes assist, but these tools are not universally available [26].

Tuberculosis and HIV coinfection: a distinct pathophysiologic context

The HIV epidemic reshaped TB epidemiology and pathogenesis. TB–HIV coinfection requires distinct consideration because immune function is fundamentally altered [27][28][15][29]. People living with HIV are about nineteen times more likely to develop active TB than those without HIV [12]. Antiretroviral therapy reduces risk but does not fully restore immune competence. TB remains the leading cause of death among people living with HIV worldwide. The burden is greatest in low resource regions where TB prevalence is high and access to integrated diagnosis and treatment is limited. HIV increases TB risk through several pathways. After exposure to Mycobacterium tuberculosis, people living with HIV have higher rates of progressive primary disease within the first year. Reactivation of latent infection also occurs more frequently. Susceptibility increases as CD4 positive T cell counts decline, reflecting the central role of these cells in granuloma maintenance and intracellular control of bacilli [15]. The precise mechanisms remain incompletely defined [28]. Proposed explanations include depletion of TB specific CD4 cells, impaired CD8 responses, dysregulated cytokine signaling, altered macrophage function, and breakdown of coordination between innate and adaptive immunity. HIV therefore disrupts immune structure and communication rather than simply reducing cell numbers [27][28][15][29].

Antiretroviral therapy introduces additional complexity through immune reconstitution. As viral replication is suppressed and CD4 counts recover, TB specific immune responses may rebound. In some patients this triggers TB immune reconstitution inflammatory syndrome. TB IRIS presents with clinical or radiologic worsening despite effective anti TB therapy. Manifestations include enlarging lymph nodes, worsening infiltrates, or new inflammatory lesions. This syndrome highlights that host inflammation can drive pathology even during microbiologic control. Clinical presentation of TB in people living with HIV varies with immune status. With preserved CD4 counts, disease often resembles that seen in HIV negative individuals. Upper lobe infiltrates and cavitation are common. Higher CD4 counts correlate with cavitary disease, likely because cavitation reflects strong immune mediated tissue destruction [27]. When CD4 counts fall below 200 cells per microliter, atypical patterns dominate. Chest radiographs may appear normal or show diffuse or lower lobe infiltrates, lymphadenopathy, or pleural effusion. These patterns delay diagnosis. Disseminated TB is also more common and may involve bloodstream infection and multiple organs. Postmortem studies indicate that disseminated TB is frequently missed in this population [15]. Early detection and treatment of TB–HIV coinfection is essential [30]. Care requires integrated screening, rapid diagnostics, timely initiation of therapy, and monitoring for drug interactions and immune reconstitution events. Laboratories must use sensitive methods that detect low bacillary burden disease and resistance.

Nursing teams play a key role in adherence support, symptom monitoring, and patient education. Public health programs must integrate TB and HIV services and maintain surveillance that captures coinfection outcomes. TB pathophysiology reflects a dynamic host pathogen interaction. Infection begins with airborne exposure and alveolar deposition. Disease progression depends on macrophage survival strategies, T cell driven granuloma formation, containment, latency, dissemination, or reactivation [14][15][16]. Cavitary disease drives transmission and complications such as hemoptysis and resistance [23]. HIV coinfection amplifies risk and alters every stage of this process. Effective control depends on integrated clinical and public health action informed by these mechanisms [27][28][15][29][12][30].

Histopathology

On routine histopathologic examination, tissue infected with Mycobacterium tuberculosis often demonstrates granulomatous inflammation that may appear either necrotizing or non-necrotizing on hematoxylin and eosin (H&E)–stained sections. Although granulomas are a characteristic tissue response in tuberculosis, they are not pathognomonic, and their presence must be interpreted in conjunction with clinical context, radiologic findings, microbiologic testing, and epidemiologic risk. Microscopically, a classic tuberculous granuloma is typically organized in concentric cellular zones. The outermost layer frequently consists of a rim of lymphocytes, often admixed with plasma cells, reflecting an adaptive immune response directed against persistent intracellular antigen. More centrally, a peripheral band of epithelioid histiocytes—activated macrophages with elongated, pale cytoplasm—forms the principal structural framework of the granuloma. Multinucleated giant cells, commonly of the Langhans type with nuclei arranged in a peripheral or horseshoe configuration, may also be present within this histiocytic zone, indicating ongoing macrophage activation and cellular fusion in response to difficult-to-eradicate organisms. A central area of necrosis may be present and, when observed, is often described as “caseous” because of its gross, cheese-like appearance. Histologically, this necrotic center may appear as amorphous, eosinophilic, acellular debris, sometimes accompanied by karyorrhectic nuclear fragments. The extent of caseation can vary with host immune status, anatomical site, and disease chronicity; in some immunocompromised patients, granulomas may be poorly formed or necrosis may be less conspicuous, which can complicate pathologic interpretation. In addition, fibrosis may be seen at the periphery of granulomas in more chronic lesions, reflecting tissue remodeling and attempts at containment. Direct demonstration of organisms provides greater diagnostic specificity but is often limited by the low bacillary burden typical of many TB lesions. When bacilli are sufficiently abundant, acid-fast organisms can be identified using the Ziehl–Neelsen stain. However, because organisms may be sparse and unevenly distributed, sensitivity is improved by fluorescent microscopy with auramine–rhodamine staining, which can facilitate detection by making bacilli more readily visible against a dark background. Even with enhanced staining methods, a negative stain does not exclude tuberculosis, and correlation with culture and molecular testing remains essential for definitive diagnosis and for guiding antimicrobial management [28][29][30].

History and Physical

Tuberculosis often presents constitutional symptoms that lack specificity. This feature drives ongoing diagnostic difficulty across clinical settings. Common manifestations include persistent cough fever weight loss night sweats and fatigue. These symptoms overlap with viral infections bacterial pneumonia malignancy and chronic inflammatory lung disease. In high prevalence regions this symptom pattern prompts early consideration of TB. In low prevalence settings clinicians may favor more common diagnoses. Limited exposure to TB lowers clinical suspicion and delays evaluation. Diagnostic delay prolongs infectiousness and allows disease progression. Mild or atypical symptoms increase this risk. Clinical assessment begins with a detailed history. Symptom review alone is insufficient. Epidemiologic and host risk factors are essential. Clinicians should ask about prior TB infection or disease known exposure to active TB and recent close contacts. Country of origin and time since migration from high burden regions matter. Travel history with prolonged indoor exposure increases risk. Family history reflects shared

exposure rather than inheritance. Occupational and residential histories identify risk in congregate settings such as hospitals laboratories long term care facilities shelters prisons dormitories and overcrowded housing. Immunosuppression must be assessed systematically. HIV infection transplantation chronic corticosteroid use chemotherapy and biologic agents such as TNF antagonists increase progression risk and promote atypical or disseminated disease. Routine inclusion of these questions improves early recognition and reduces missed opportunities for isolation testing and treatment [30][31].

Physical findings depend on disease stage. Latent TB causes no symptoms or exam abnormalities. Early active TB may also lack findings. Normal examination does not exclude disease. As pulmonary TB progresses symptoms often develop gradually. Cough may evolve from dry to productive. Fever night sweat fatigue and weight loss become prominent. Hemoptysis may occur and often signals advanced cavitary disease. Lung examination varies widely. Early disease may produce no abnormal sounds. More extensive disease can reveal bronchial breath sounds crackled or signs of consolidation. Cavitation may be clinically silent and detected only on imaging. Chronic untreated TB leads to structural lung damage. Extensive cavitation and fibrosis distort lung architecture. Long term disease may produce visible chest wall deformities due to volume loss [31]. Extrapulmonary TB adds complexity. It can involve lymph nodes pleura bone kidneys central nervous system or genitourinary tract. Respiratory symptoms may be absent. Presentation depends on the affected organ. These features demand integration of constitutional symptoms epidemiologic risk immune status and focused organ examination. Persistent unexplained inflammation in at risk individuals should always raise concern for TB [31].

Evaluation

Tuberculosis (TB) remains one of the most diagnostically demanding infectious diseases in contemporary clinical practice, largely because its clinical manifestations are protean, its microbiologic confirmation can be slow or elusive, and its epidemiologic context varies dramatically across regions and patient populations. The evaluation of a patient for TB is not a single, uniform diagnostic pathway; rather, it is a set of related approaches that diverge according to the clinical question—latent infection, active pulmonary disease, or extrapulmonary disease—and the resources and prevalence context in which care is delivered.[32][5] In high-burden settings, the pretest probability for TB is often substantial, and diagnostic algorithms are designed to identify infectious cases rapidly and at scale, sometimes accepting imperfect sensitivity in exchange for feasibility. In low-burden settings, the pretest probability is lower, and the diagnostic emphasis often shifts toward specificity, careful risk stratification, and avoiding unnecessary treatment while still preventing missed cases that could drive outbreaks. Across all settings, the ideal evaluation integrates radiology, microbiology, molecular diagnostics, biomarkers, and immunologic testing, recognizing that no single test is sufficient in every clinical scenario and that the interpretation of all results must be contextualized within host immune function and epidemiologic risk. A central principle in TB evaluation is that test performance is not fixed in the abstract; sensitivity and specificity are strongly influenced by factors such as the patient's immune status, age, timing relative to exposure or symptom onset, the quality of specimen collection, adherence to standardized laboratory procedures, and the clinician's ability to interpret results in relation to pretest probability. This is particularly relevant in TB because the disease is often paucibacillary, can be localized in sites that are difficult to sample, and may present with nonspecific imaging and systemic symptoms. Consequently, radiologic findings may range from normal to markedly abnormal without offering a pathognomonic signature, and laboratory tests may be negative even in true disease due to specimen limitations or low organism burden. In the absence of confirmatory culture or molecular evidence, TB diagnoses may be presumptive and based on the convergence of clinical suspicion, imaging patterns, epidemiologic risk, and surrogate markers of infection. Under-diagnosis and over-diagnosis occur in parallel, and the direction of bias often reflects the surrounding epidemiologic setting: in high-prevalence regions, clinicians may treat empirically to avoid missing contagious disease, whereas in low-prevalence regions, clinicians may undervalue TB in the differential, delaying evaluation until disease is advanced.[17][32][33][34][35][36] These realities underscore why the evaluation process is best

conceptualized as iterative and probabilistic, with results repeatedly re-integrated as new information becomes available, rather than as a single linear test sequence .[17][32][33][34][35][36].

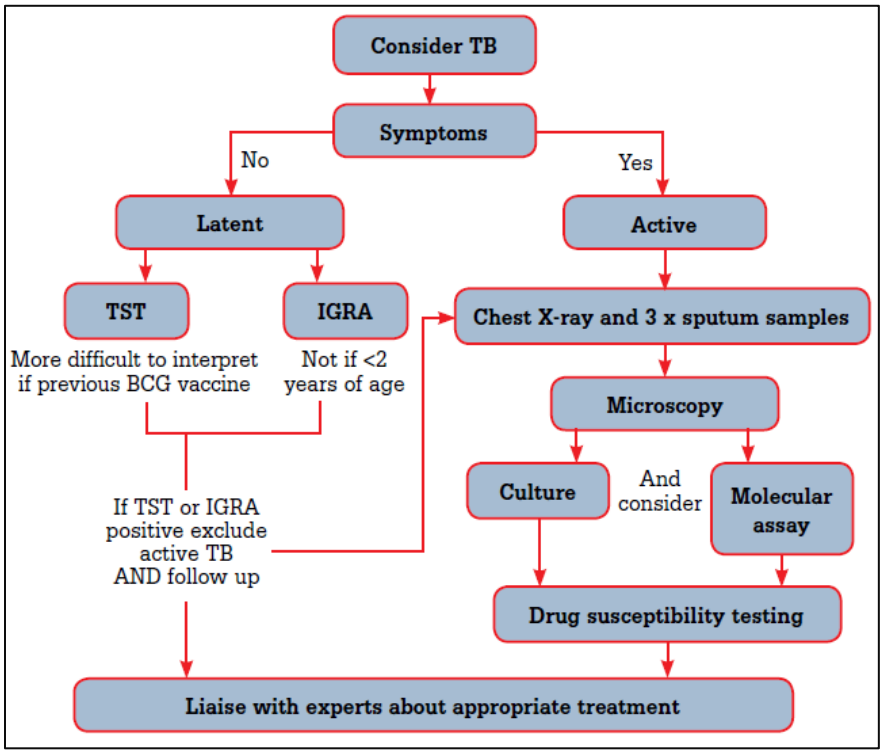

Fig. 3: Diagnosis of Tuberculosis.

Evaluation for latent tuberculosis infection

Evaluation of latent tuberculosis infection focuses on prevention. The goal is to identify people with immunologic evidence of infection who face meaningful risk of progression to active disease. Latent TB causes no symptoms and poses no transmission risk. Testing therefore targets defined populations rather than the general public in low burden settings. Priority groups include people living with HIV, close contacts of patients with active TB, and individuals expected to receive immunosuppressive therapy. This group includes candidates for anti–tumor necrosis factor agents, patients on dialysis, and those preparing for solid organ or bone marrow transplantation. Additional risk arises from occupational or environmental exposure such as silicosis, which strongly increases TB susceptibility. Screening also expands in settings with higher background prevalence or structural vulnerability linked to poverty migration incarceration unstable housing or limited healthcare access. Detection matters only when it enables preventive therapy that lowers future disease risk and supports population level control. Available tests include the tuberculin skin test, interferon gamma release assays, and newer tuberculosis specific antigen skin tests [37][5]. Test selection depends on cost feasibility and health system capacity. In the United States IGRAs are preferred, while the skin test remains acceptable when resources limit access. In low and middle income countries the World Health Organization supports either approach based on local context [5]. The most accurate test may fail if supply chains staffing or follow up are unreliable [37]. The tuberculin skin test remains widely used because it is inexpensive and simple. Its limitations are substantial. False negatives occur early after infection and in immunocompromised patients. Technique and reading errors affect accuracy. False positives result from prior BCG vaccination or exposure to nontuberculous mycobacteria. IGRAs improve specificity by avoiding BCG cross reactivity and reduce loss to follow up by eliminating return visits. Sensitivity improves in HIV but declines with severe immunosuppression. Indeterminate results occur in young children and in patients with low CD4 counts [34]. TB specific antigen skin tests aim to combine simplicity

with higher specificity [37][5]. They still require return visits and may carry high costs. No immunologic test distinguishes latent from active TB or predicts progression. Active disease must always be excluded before preventive therapy. Clinical judgment integrates test results risk factors and potential treatment harm. Probability based tools such as the Online TST IGRA Interpreter support this process but do not replace clinician decision making [39].

Evaluation for active tuberculosis disease: principles and challenges

The evaluation of active TB differs fundamentally from latent infection assessment because the clinical priority is immediate: to confirm disease, identify infectiousness, initiate appropriate multi-drug therapy, and detect drug resistance early enough to prevent treatment failure and ongoing transmission. A gold standard for active TB diagnosis is microbiologic confirmation by culture. Yet in many clinical contexts, culture confirmation is difficult to obtain in a timely manner and may be negative even in true disease due to limited specimen quality, low organism burden, or extrapulmonary localization. The slow growth of Mtb further delays culture results, which can constrain clinical decision-making in urgent scenarios. Therefore, while culture remains foundational for definitive diagnosis and drug susceptibility testing, active TB diagnosis is often presumptive in practice and rests on a composite of pretest probability, supportive imaging, molecular assays, biomarker patterns, and clinical evolution under therapy. Because signs and symptoms of TB are nonspecific, evaluation begins with a careful appraisal of epidemiologic risk and clinical presentation, followed by a structured diagnostic strategy. In high-prevalence settings, a persistent cough with systemic symptoms may justify rapid diagnostic testing and empiric treatment while awaiting confirmation, especially when the public health risk of transmission is high. In low-prevalence settings, clinicians may pursue broader differential diagnosis evaluation while simultaneously testing for TB if risk factors are present. The resource environment shapes these decisions profoundly: availability of molecular assays, radiologic modalities, and laboratory capacity determines how quickly a presumptive diagnosis can be converted into microbiologic confirmation [38][39].

Imaging in suspected active tuberculosis

Imaging supports tuberculosis evaluation by revealing suggestive patterns, mapping disease extent, identifying complications, and guiding diagnostic sampling. Imaging alone does not confirm TB. Chest radiography remains the first step in many systems because it is accessible, low cost, and fast. Despite this role, chest x rays may appear normal in active disease. This occurs in early infection, selected extrapulmonary forms, and profound immunosuppression. Computed tomography offers higher sensitivity and clearer anatomic detail and often detects abnormalities missed on radiography. Magnetic resonance imaging and positron emission tomography combined with CT serve focused indications, especially extrapulmonary disease and selected assessments of treatment response using FDG PET CT [40]. Modality choice depends on clinical questions, patient factors, and resource availability, with different priorities for pulmonary, disseminated, or localized disease. Interpretation often refers to disease stage, yet patterns overlap. Primary TB may show parenchymal infiltrates or atelectasis, commonly in middle or lower lung zones, though only a minority of cases display clear findings. Intrathoracic lymphadenopathy appears more often in children and in people living with HIV, reflecting immune and distribution differences. Healed infection can leave calcified Ghon foci or Ranke complexes. Pleural effusion occurs less often and is usually unilateral, with higher frequency in some immunocompromised groups. Miliary disease reflects hematogenous spread and appears infrequently overall but more often in infants, older adults, and severely immunocompromised patients. Primary TB may still present with a normal chest x ray, while CT can reveal subtle parenchymal or nodal disease not seen on radiography [38][39][40]. Post primary TB commonly shows patchy consolidation in upper lobe apical and posterior segments and in superior lower lobe segments. Cavitation affects many adults but remains uncommon in young children and in severe immunosuppression. Adenopathy is less prominent in immunocompetent adults. Endobronchial spread produces a tree in bud pattern on CT, reflecting airway centered infection. Pleural effusion and miliary disease remain uncommon but appear in high risk groups. HIV coinfection complicates interpretation,

particularly when CD4 counts fall below 200 cells per microliter. Lymphadenopathy becomes prominent, cavitation less frequent, and extrapulmonary disease more common. Patterns may appear atypical or even normal, which delays recognition in low burden settings. Chronic disease shows cavitation, fibrosis, bronchiectasis, and rare bronchopleural fistulae. Imaging cannot reliably separate active from inactive disease because residual abnormalities persist after cure. Microbiologic confirmation remains essential. Imaging refines probability and directs sampling and targeted evaluation [40][36].

Microscopy, culture, and molecular analysis in suspected active TB

When clinical suspicion for active TB exists, microbiologic evaluation becomes obligatory, both to establish diagnosis and to guide management. Conventional approaches rely on acid-fast bacilli (AFB) smear microscopy and culture from sputum or other appropriate specimens. Historically, staining and culture have been the primary confirmatory tools, but modern evaluation increasingly integrates automated real-time nucleic acid amplification tests (NAATs) and biomarker-based probes that accelerate detection and can identify drug resistance early.[41][42][43] Even with these advances, specimen acquisition remains the practical bottleneck in many cases. Patients may be unable to produce adequate deep sputum, extrapulmonary sites may require invasive sampling, and bacillary burden may be low. These limitations explain why active TB is often treated presumptively in high-risk scenarios while confirmation is pursued in parallel. AFB smear microscopy remains widely used because it is relatively rapid and can be scaled in resource-constrained environments, but its sensitivity is variable and often limited by the paucibacillary nature of TB and by specimen quality. Reported smear sensitivity ranges from 34% to 80%.[35] Multiple strategies can improve sensitivity, including the use of fluorochrome stains, specimen concentration techniques, and ensuring larger sputum volume—often cited as at least 5 mL. Respiratory specimen acquisition methods that access lower airway secretions more directly, such as induced sputum or bronchoscopy, can improve diagnostic yield, and gastric lavage may be useful in certain patients, particularly children, who swallow sputum rather than expectorate.[44] Traditional practice in some settings involves collecting sputum specimens on three separate days to improve sensitivity, but this approach is debated, especially in resource-poor regions where repeated visits and specimen handling can be burdensome and may not yield proportional benefit.[45] Variations in technique and interpretation—reflecting limited standardization—likely contribute to heterogeneous performance and practice patterns across laboratories.[46] Importantly, smear performance is strongly influenced by pretest probability; sensitivity tends to be higher in regions with higher TB prevalence and among patients with advanced cavitary disease [42][43][44][45][46].

Conclusion:

Tuberculosis exemplifies the intersection of microbiology, clinical medicine, and social determinants of health. Despite major scientific advances, TB continues to impose a global burden due to diagnostic delays, prolonged treatment, and structural inequities. The persistence of latent infection, coupled with rising drug resistance and HIV coinfection, underscores the complexity of eradication efforts. While molecular diagnostics and shorter regimens represent progress, their benefits are unevenly distributed, particularly in high-burden, resource-limited settings. Sustainable TB control requires more than technological innovation; it demands health system strengthening, equitable access to care, and coordinated interprofessional practice. Laboratory professionals play a pivotal role in accurate diagnosis and resistance detection, nurses ensure adherence and patient education, and epidemiologists guide surveillance and targeted interventions. Achieving WHO's ambitious targets will depend on integrating these disciplines within a framework that addresses both biomedical and social drivers of disease. Ultimately, TB control is not a static achievement but a dynamic, adaptive process requiring continuous investment, global collaboration, and commitment to equity. Without these measures, TB will remain a defining challenge of public health in the 21st century.

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