Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/202522373

Latent Tuberculosis Infection: Integrated Laboratory Diagnostics and Public Health–Epidemiologic Strategies for Detection, Surveillance, and Prevention

Maram Hassan Almuzaini [(1)] , Abdulrahman Mohammed Ali Munthiri [(2)] , Ali Mohammed Al Amer [(3)] , Fatema Ibrahim Aqeeli [(4)] , Asmaa Suliman Hadi Thaker [(4)] , Faisal Razhan Mohamed Alshehri [(5)] , Sami Mohammed Alharbi [(6)] , Najla Dakel Salemaljam [(7)] , Waleed Ali Ahmed Maghfuri [(8)] , Abdullah Mohammed Abdullah Alomi [(9)] , Munirah Falah Zidan Alazmi [(10)] , Abdullah Essa Magbol Oraybi [(11)] , Khaled Saud Alharbi [(12)]

(1) Ministry Of Health, Saudi Arabia,
(2) Ministry of Education / Jazan University – Jazan University Hospital, Saudi Arabia,
(3) Al Ha'ir Health Center,Ministry of Health, Saudi Arabia,
(4) Jeddah Health Cluster 2 Administration – Al-Wafa Health Center (Jeddah),Ministry of Health, Saudi Arabia,
(5) Kindergarten Health Center 1, Riyadh,Ministry of Health, Saudi Arabia,
(6) Forensic Toxicology Services Department,Ministry of Health, Saudi Arabia,
(7) Maternity & Children's Hospital, Hafr Al-Batin,Ministry of Health, Saudi Arabia,
(8) King Abdullah Hospital, Bisha,Ministry of Health, Saudi Arabia,
(9) King Khalid University Hospital,Ministry of Health, Saudi Arabia,
(10) Qurayyat Mental Health Hospital, Al-Jouf Health Cluster – Ministry of Health, Saudi Arabia,
(11) General Season Hospital, Jazan,Ministry of Health, Saudi Arabia,
(12) King Fahad Specialist Hospital in Qassim ,Ministry of Health, Saudi Arabia

Abstract

Background: Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health challenge, with latent tuberculosis infection (LTBI) serving as a critical reservoir for future active disease. Approximately one-third of the world's population is infected, yet most remain asymptomatic, creating diagnostic and preventive complexities.

Aim: To review integrated laboratory diagnostics and public health strategies for LTBI detection, surveillance, and prevention, emphasizing risk stratification and safe treatment practices.

Methods: This narrative review synthesizes current evidence on LTBI epidemiology, pathophysiology, diagnostic modalities—including tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—and management approaches. It draws on global guidelines and recent studies addressing diagnostic limitations, treatment efficacy, and toxicity mitigation.

Results: LTBI diagnosis relies on immune-based tests interpreted within clinical and epidemiologic context, as neither TST nor IGRA distinguishes active disease. Chest radiography and sputum analysis remain essential to exclude active TB. Preventive regimens—isoniazid monotherapy (6–9 months), rifampicin monotherapy (3–4 months), or rifamycin–isoniazid combinations—reduce progression risk by 60–90%. However, hepatotoxicity and adherence challenges necessitate individualized risk–benefit assessment, baseline liver monitoring, and patient education. Emerging biomarkers and shorter regimens promise improved precision and completion rates.

Conclusion: Effective LTBI control requires integrated diagnostics, targeted treatment, and interprofessional collaboration. Advances in biomarker research and patient-centered strategies are pivotal for optimizing prevention and minimizing harm.

Keywords: Latent tuberculosis infection, LTBI, interferon-gamma release assay, tuberculin skin test, preventive therapy, hepatotoxicity, public health

Introduction

Mycobacterium tuberculosis remains one of the most consequential bacterial pathogens affecting human health worldwide. Although it is classically associated with pulmonary disease, the organism has the capacity to disseminate hematogenously or via lymphatic pathways to virtually any organ system, producing a broad spectrum of clinical phenotypes that include acute disease, chronic progressive illness, and latent infection. This biological versatility underpins tuberculosis as both a clinical challenge and a public health priority, as the same pathogen can manifest with variable transmissibility and morbidity depending on host immune status, environmental conditions, and healthcare access. [1] Tuberculosis is a global disease, but its distribution is markedly

*Corresponding author e-mail: Mhalmuzaini@Moh.Gov.Sa (Maram Hassan Almuzaini).
Receive Date: 28 November 2025, Revise Date: 23 December 2025, Accept Date: 24 December 2025

inequitable. The burden falls disproportionately on low-income countries and on populations facing structural vulnerability within all settings. Individuals who are homeless or unsheltered, those who are incarcerated, and people who use intravenous drugs experience elevated exposure risk, higher prevalence of comorbidities, and reduced access to consistent preventive and curative services. These factors contribute to delayed diagnosis, incomplete treatment, and ongoing community transmission. Beyond clinical morbidity, the economic consequences of tubercular illness are substantial: costs related to evaluation, prolonged therapy, time away from work, and downstream complications can be financially catastrophic, consuming household resources and threatening livelihoods—particularly in populations already subject to economic insecurity. [2][3] In high-income countries where overall tuberculosis prevalence is low, the epidemiologic profile of disease tends to be characterized by clustered transmission, imported infections, and reactivation from latent states rather than widespread ongoing community spread. Accordingly, public health strategies increasingly emphasize the identification and treatment of latent tuberculosis infection (LTBI) as a cornerstone of tuberculosis control and elimination efforts. This approach is grounded in the understanding that LTBI represents a reservoir of viable organisms contained by the host immune system, which may later reactivate and progress to active, infectious disease. Preventing reactivation through targeted testing and treatment can therefore reduce incident active TB cases and limit secondary transmission, yielding benefits that extend beyond the individual patient to the broader population. [4] Nevertheless, effective LTBI programs require more than simply expanding testing. Public health and laboratory professionals must jointly ensure accurate identification of infected individuals while also determining who is at greatest risk of progression to active disease. This risk stratification is essential because preventive therapy, although effective, carries potential harms, including medication toxicity, drug–drug interactions, and challenges with adherence over prolonged regimens. Consequently, the decision to treat latent infection demands careful balancing of anticipated benefit—averting active TB and its associated transmission—against the probability and severity of adverse effects. Within this framework, the characterization of LTBI is not merely a diagnostic exercise but an integrated public health intervention requiring coordinated laboratory diagnostics, epidemiologic assessment, and equitable access to preventive care [2][3][4].

Etiology

Tuberculosis is caused by infection with *Mycobacterium tuberculosis*, a pathogenic member of the genus *Mycobacterium* and the principal agent responsible for human TB disease. Although *M. tuberculosis* is the canonical etiologic organism, it exists within a broader genus that includes numerous nontuberculous mycobacteria (NTM), many of which are environmental organisms capable of causing opportunistic disease. Distinguishing *M. tuberculosis* complex from NTM is essential for both clinical management and public health, as transmission dynamics, infection-control requirements, treatment regimens, and reporting obligations differ substantially between these groups. A defining structural feature shared by mycobacteria is their bacillary morphology and a highly specialized cell envelope enriched with mycolic acids. This lipid-dense outer layer contributes to environmental persistence, resistance to desiccation, and reduced permeability to many antimicrobial agents, thereby shaping both pathogenicity and therapeutic complexity. [5] The same cell envelope also explains key laboratory properties of *M. tuberculosis*. Because the high mycolic acid content limits uptake of conventional dyes, mycobacteria are not reliably visualized with the standard Gram stain, which renders them difficult to detect using routine bacteriologic microscopy. Instead, light microscopic identification generally requires acid-fast staining methods that exploit the organism's ability to retain certain dyes despite decolorization with acid-alcohol. Commonly used techniques include auramine-rhodamine fluorescent staining, which enhances sensitivity through fluorescence microscopy, and the Ziehl–Neelsen stain, a classic method that demonstrates acid-fast bacilli as brightly stained organisms against a contrasting background. These stains do not confirm species identity on their own, but they provide an important initial indication of mycobacterial infection and help triage specimens for culture and molecular testing. [6][7]

From a microbiologic growth standpoint, mycobacteria are obligate aerobes and characteristically slow-growing organisms. The slow replication rate of *M. tuberculosis* has practical implications for laboratory workflows, clinical decision-making, and public health response, because culture confirmation can require prolonged incubation—often extending over several weeks—before a definitive positive result is obtained. This delay historically contributed to diagnostic uncertainty and may impede timely initiation of targeted therapy or contact investigations if culture is relied upon exclusively. [8] When culture growth is achieved, identification of *M. tuberculosis* has traditionally depended on a combination of morphologic appearance and biochemical characteristics of the isolate. However, contemporary diagnostic algorithms increasingly incorporate rapid molecular methods to shorten time to organism identification and to inform early therapeutic choices. Nucleic acid amplification testing (NAAT), for example, can identify *M. tuberculosis* directly from

clinical specimens or from cultured isolates and may simultaneously target genetic loci associated with drug resistance, thereby supporting earlier optimization of treatment regimens and more effective infection-control strategies. Such rapid diagnostics are particularly valuable in settings where multidrug-resistant TB is a concern or where delays in phenotypic susceptibility testing could carry major clinical and epidemiologic consequences. [7]

Epidemiology:

Tuberculosis remains one of the most consequential infectious diseases worldwide, with an epidemiologic footprint that reflects both widespread latent infection and persistent mortality. It is estimated that approximately one-third of the global population is infected with *Mycobacterium tuberculosis*, underscoring the extraordinary scale of the latent reservoir from which future active disease may emerge. Although tuberculosis is, in principle, both treatable and curable with effective antimicrobial therapy, it continues to cause substantial loss of life, with approximately 1.5 million deaths reported annually on a global scale. [9] This apparent paradox—high curability yet high mortality—highlights the central role of delayed diagnosis, barriers to care, treatment interruption, and the compounding effects of comorbidities and social vulnerability. The global burden of tuberculosis is not evenly distributed. Instead, infection and disease are concentrated in low-income settings, where structural determinants such as crowded housing, under-resourced health systems, limited access to diagnostics, and constrained treatment capacity amplify transmission and worsen outcomes. High rates of infection, described as exceeding 300 cases per 100,000 population per year, are reported in India and in several countries in sub-Saharan Africa, reflecting intense transmission in communities already burdened by poverty and limited healthcare infrastructure. [2] In Eastern Europe, incidence rates are also substantial, with estimates reaching as high as 154 per 100,000 population per year, emphasizing that tuberculosis remains a major public health challenge even outside traditionally high-burden tropical region. [2]

In contrast, countries characterized as having relatively low incidence—such as the United States—are described as having tuberculosis incidence below 100 per 100,000 population per year. [9] In these settings, the epidemiologic pattern often shifts from generalized community transmission to more focal risks, including importation and reactivation. Notably, a large proportion of tuberculosis cases in the United States occur among individuals born outside the country, consistent with the contribution of prior exposure in higher-incidence regions and the subsequent reactivation risk after migration. Sex-based differences in tuberculosis epidemiology are also observed. Incidence is generally higher among males than females; for example, one study reported pulmonary TB rates of 31.8 cases per 100,000 person-years in males compared with 20.1 cases per 100,000 person-years in females. [10] In parallel, HIV coinfection continues to shape global risk profiles, with approximately 12% of newly diagnosed tuberculosis occurring in people living with HIV. [11] This intersection has diagnostic and programmatic implications because the performance and interpretation of interferon-gamma–based testing may be influenced by the degree of HIV-associated immunosuppression, complicating the identification of latent infection and risk assessment in immunocompromised populations. [12][13] Following inhalational exposure to *M. tuberculosis*, only a minority of infected individuals develop active disease, with lifetime progression estimates commonly cited at approximately 5% to 15%. [14][15] Latent infection may persist for decades, yet epidemiologic data consistently indicate that the highest risk of progression occurs relatively early, with many cases that progress to active disease doing so within the first two years following exposure. [14][15] This temporal pattern reinforces the public health importance of early identification of latent infection in high-risk groups and timely delivery of preventive therapy to reduce both individual morbidity and downstream transmission.

Pathophysiology

Transmission of *Mycobacterium tuberculosis* occurs predominantly via inhalation of aerosolized droplet nuclei that reach the terminal airways and alveoli. Once deposited, the organism encounters host defenses that vary substantially between individuals, producing a range of immunologic and clinical outcomes. In some hosts—particularly those who are immunocompetent—the earliest containment may involve efficient phagocytosis and killing by alveolar macrophages, leading to complete elimination of the bacillus before durable infection is established. In other individuals, however, innate immune mechanisms are insufficient to sterilize the infection, and the lung mounts a structured granulomatous response designed to contain, rather than eradicate, the organism. This granulomatous lesion, termed a tubercle, represents a coordinated cellular architecture in which macrophages, epithelioid cells, and lymphocytes organize around infected foci to restrict bacterial replication and prevent dissemination. [16] The ensuing host–pathogen relationship is best conceptualized as a continuum rather than a binary state. Clinical phenotypes range from latent tuberculosis infection to active tuberculosis disease, and this spectrum reflects the degree to which bacilli remain sequestered within granulomas versus escaping containment through dynamic interactions between bacterial fitness and host immune pressure. [17][16] Granulomas are not static structures; they evolve over time, influenced by immune signaling,

local tissue microenvironments, and bacterial persistence strategies. When the host response successfully maintains control, viable organisms may persist in a constrained state without clinical disease, establishing latency. Conversely, when immune containment fails—whether abruptly or gradually—bacilli may proliferate, tissue necrosis may develop, and organisms may access airways and be transmitted, producing active disease that is both clinically apparent and potentially infectious.

Early after infection, a transient bacteremic phase may occur, and this phenomenon appears particularly relevant in individuals with impaired cellular immunity, including those with HIV. During bacteremia, mycobacteria can disseminate hematogenously and seed distant organs, providing a mechanistic basis for extrapulmonary tuberculosis involving lymph nodes, bone, central nervous system, genitourinary tract, and other sites. [18] Importantly, dissemination does not necessarily imply immediate clinical disease; seeding may remain clinically silent for prolonged periods until immune control wanes. Within this framework, latent TB infection is defined operationally as evidence of an immunologic response to *M. tuberculosis*—typically via immunodiagnostic testing—without evidence of clinical disease. [19] This definition highlights a core challenge for laboratory and public health practice: latency is inferred by immune recognition rather than directly measured bacterial burden, and it therefore represents a state of risk rather than a fixed biologic endpoint. In the absence of treatment, the lifetime risk of reactivation from latent TB infection is estimated at approximately 5% to 15%, although this aggregate figure obscures substantial heterogeneity across populations and contexts. [20] Reactivation risk is not uniform; it is shaped by coincident pathogen exposures, host immune integrity, and environmental and social conditions that influence both susceptibility and progression. At the bacterial level, pathogenic determinants include differences in virulence among clades of *M. tuberculosis* that have co-evolved with human host populations, as well as variation in progression to active disease among species within the *M. tuberculosis* complex. [14] Such differences imply that the likelihood of persistence, immune evasion, and progression may vary by lineage, potentially affecting transmission patterns and clinical epidemiology at the population level.

Host determinants are often the most clinically actionable drivers of progression. Immunosuppression is a dominant risk factor, and advancing age contributes through multiple mechanisms, including age-related decline in immune responsiveness, alterations in innate immune recognition (including mutations in Toll-like receptors), T-cell depletion, and shifts in cytokine signaling such as interferon-gamma and tumor necrosis factor. [9] These changes reduce the capacity to sustain granuloma stability and to maintain effective macrophage activation, thereby increasing the probability that contained organisms will resume replication. Iatrogenic immunomodulation further amplifies risk. Patients receiving biologic therapies for rheumatologic diseases may have elevated reactivation risk because these agents disrupt cytokine pathways central to cellular immunity and granuloma maintenance. [21] Additional conditions associated with impaired immune defense and increased progression to active TB include HIV infection, diabetes, smoking, malignancy, corticosteroid use, and solid organ or hematological transplantation. [21] Each of these factors can diminish immune surveillance or alter inflammatory signaling, thereby lowering the threshold at which latent infection transitions to active disease. Taken together, the pathophysiology of latent and active tuberculosis reflects a dynamic equilibrium between a pathogen capable of long-term persistence and a host immune system that may contain but not sterilize infection. The clinical and public health implications are direct: identifying latent infection is necessary but not sufficient; determining who is most likely to progress requires integrating host risk factors, potential bacterial lineage effects, and environmental context. Bacterial variation—including clade-specific virulence and differences across the *M. tuberculosis* complex—remains an important contributor to this heterogeneity and reinforces that progression is not solely a function of exposure intensity, but of the evolving biology of both host and pathogen. [14]

History and Physical

Latent tuberculosis infection (LTBI) is, by definition, a clinically silent state. Individuals with LTBI are asymptomatic and do not exhibit the constitutional or respiratory features that characterize active disease. [19] Consequently, history-taking in the setting of LTBI evaluation is inherently dual-purpose: it must first identify individuals for whom testing is indicated based on epidemiologic and clinical risk, and it must simultaneously exclude signs or symptoms suggestive of active tuberculosis, which would necessitate a fundamentally different diagnostic and infection-control pathway. For laboratory specialists and public health professionals, this dual objective is central because inappropriate testing of symptomatic individuals as “latent” can delay recognition of infectious disease and undermine transmission control. Indications for LTBI testing are anchored in risk stratification, which differs by local TB incidence. In low-incidence settings, testing is prioritized for individuals at elevated risk of reactivation and those at heightened likelihood of recent exposure or new infection. In high-incidence settings, testing may also be directed toward individuals at moderate-to-high risk of progression, where preventive therapy can yield meaningful

reductions in incident active TB. [22] A rigorous medical and social history is therefore essential, focusing on both host susceptibility and exposure probability. Risk factors that substantially increase the likelihood of reactivation include conditions and treatments that impair cellular immunity or granuloma stability. These include a personal history of hematologic or solid organ transplantation, chronic dialysis dependence, silicosis, the use of anti–tumor necrosis factor (anti-TNF) therapies, and HIV coinfection. [21] Because LTBI represents a reservoir with variable propensity to progress, documenting these factors is not merely descriptive; it directly informs the urgency of testing, the threshold for initiating preventive therapy, and the intensity of follow-up.

Exposure history is equally important, particularly recent or ongoing contact with infectious pulmonary TB. Individuals of all ages who have close contact with a patient with active TB disease are at substantially increased risk of acquiring infection and may require prompt evaluation and follow-up testing. Contact investigations often depend on precise characterization of the nature, intensity, and duration of exposure, including household contact, congregate living exposure, or workplace exposure. In parallel, history should incorporate epidemiologic contexts associated with higher baseline exposure risk, including incarceration, healthcare employment, homelessness or unstable housing, illicit drug use, and occupational or environmental exposures such as silica that both increase risk of infection and predispose to progression. In addition, migration history is critical: individuals who have emigrated from high-incidence regions to low-incidence countries contribute disproportionately to TB case burden through reactivation, and travel or residency patterns can shape both exposure likelihood and testing priorities. [4][23][24] Because LTBI evaluation must exclude active disease, symptom screening should be explicit and structured. Symptoms suggestive of active pulmonary TB include cough persisting longer than two weeks, dyspnea, hemoptysis, and pleuritic or non-pleuritic chest pain. Systemic features—fever, night sweats, and unintentional weight loss—are also classic indicators of active disease and should be assessed carefully, including duration and trajectory. [22]

In settings where symptom reporting may be limited by stigma, fear of exclusion from work, or limited health literacy, clinicians and public health workers should use clear, culturally sensitive questioning to improve accuracy and reduce underreporting. The physical examination, while often normal in LTBI, should be directed toward identifying clinical signs of active disease, including both pulmonary and extrapulmonary manifestations. General appearance and vital signs provide immediate clues: cachexia or visible weight loss, fever, and diaphoresis may support concern for active infection. While “sputum jars of hemoptysis” is not a standard examination finding, visible evidence of hemoptysis or reports corroborated by observation should increase urgency for evaluation as potential active pulmonary TB. Extrapulmonary TB can present with lymphadenopathy, skin findings such as erythema nodosum or panniculitis, pallor suggestive of anemia, and signs referable to meningeal, peritoneal, or osteoarticular involvement. [22] Because extrapulmonary presentations may be subtle, targeted examination based on symptoms—headache, neck stiffness, abdominal pain, joint pain, or focal swelling—can improve detection of clinically significant disease that may otherwise be misclassified as latent. Finally, the examination can also reveal features that increase reactivation risk and influence clinical decision-making. Intravascular catheters or arteriovenous fistulas may indicate chronic dialysis, a known risk factor for progression. Evidence of organ transplantation, immunosuppressive therapy, or steroid-related physical changes can further support a high-risk classification and justify more urgent preventive therapy consideration after active disease has been excluded. By integrating symptom screening, exposure assessment, and identification of host risk factors, the history and physical examination become the cornerstone of appropriate LTBI testing strategies and safe public health practice. [21][22]

Evaluation

Evaluation for latent tuberculosis infection (LTBI) occupies a distinctive space at the interface of laboratory medicine and public health practice because it requires a diagnosis of immunologic sensitization to *Mycobacterium tuberculosis* while simultaneously ensuring that active, potentially transmissible tuberculosis (TB) disease is not overlooked. A central principle is that no single test can accurately distinguish active TB disease from latent infection. Instead, LTBI is inferred through evidence of a cellular immune response to *M. tuberculosis* in a person who lacks clinical and radiologic findings consistent with active disease. This conceptual framework has practical implications: immune-based tests are not diagnostic of active disease, and evaluation must integrate symptom screening, risk stratification, and targeted microbiologic investigation when active TB remains plausible.

Immune-Based Testing

Immune-based assays for LTBI include the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). These tests are widely used in high-income, low-incidence settings where preventive strategies focus on identifying and treating latent infection, and where Bacille Calmette–Guérin (BCG) vaccination is less commonly used as a population-wide intervention. [25] Importantly, neither TST nor IGRA has adequate sensitivity or

specificity to diagnose active TB disease, and they should not be used for that purpose; definitive evaluation of active TB relies on mycobacterial culture and molecular diagnostics. [26] For laboratory specialists, this limitation is fundamental: immune-based tests detect host immune recognition, not viable organisms, and therefore cannot confirm infectivity or disease activity.

Tuberculin Skin Test

The TST involves intradermal administration of a purified protein derivative (PPD) tuberculin antigen preparation, designed to elicit a T-cell–mediated delayed-type hypersensitivity reaction in individuals previously sensitized to *M. tuberculosis* antigens. [27] Following recent infection, skin test conversion may require time; development of a measurable response can take up to 12 weeks, which is clinically relevant during contact investigations and serial testing protocols. [28] The immunologic basis of the test is an antigen-specific cellular response dominated by TH1 pathways, resulting in local inflammation and induration. If cellular immunity is intact and sensitization is present, the reaction produces induration with associated erythema. [30] Accurate reading requires that the patient return within an appropriate time window—commonly 2 to 5 days after placement—for measurement of induration by a trained clinician. The TST has well-recognized limitations related to both false-positive and false-negative results. It is not specific for *M. tuberculosis*. False-positive reactions may occur in individuals vaccinated with BCG, in those exposed to environmental nontuberculous mycobacteria (NTM), or in persons with historical exposure to *M. tuberculosis* who have subsequently cleared infection but retain immunologic memory. Misapplication of technique, improper intradermal placement, or misinterpretation of induration can further compromise accuracy. Cross-reactive NTMs associated with TST positivity include *Mycobacterium avium-intracellulare*, *Mycobacterium simiae*, *Mycobacterium scrofulaceum*, and *Mycobacterium kansasii*. [31][32] Of these, *M. kansasii* and the *M. avium-intracellulare* complex are clinically relevant because they can cause significant pulmonary disease, particularly in individuals with underlying structural lung pathology. [31][32] From an epidemiologic perspective, the impact of NTM on false-positive TST interpretation varies by geography. Globally, NTM is generally a less important contributor to false-positive TST results, except in settings where NTM exposure is high but *M. tuberculosis* prevalence is low—conditions that shift the pre-test probability and therefore the positive predictive value of the test. [33] False-negative TST results are also clinically important, particularly in populations targeted for LTBI screening. Immunosuppression can blunt delayed-type hypersensitivity responses, producing non-reactivity even in infected individuals. [34] Additionally, the observation that a substantial proportion of individuals with prior exposure do not respond to TST—reported as approximately 50% in some contexts—may reflect impaired TH1-driven cellular immunity, waning immune responses over time, or the possibility that exposure did not culminate in established infection. [29] For public health programs, these limitations reinforce the need for test selection based on patient factors (age, immune status, vaccination history), local epidemiology, and the consequences of false negatives in high-risk groups.

Interferon-Gamma Release Assays

IGRAs are blood-based tests that measure in vitro interferon-gamma release by sensitized T cells in response to *M. tuberculosis*–specific antigens that are not present in the BCG vaccine and are absent from most NTM species. [34][35] This antigen specificity is a key advantage in many settings because it reduces false positives attributable to BCG vaccination and most environmental mycobacteria. [36] Operationally, IGRA testing typically requires collection into three tubes: a negative control, a positive (mitogen) control such as phytohemagglutinin, and a tube containing *M. tuberculosis*–specific antigens. [27] After incubation—commonly up to 24 hours—the sample is processed and results are reported as positive, negative, or indeterminate. Compared with TST, IGRAs generally have higher specificity for *M. tuberculosis* exposure, but they may be more expensive and resource-intensive in some contexts, particularly where laboratory infrastructure or timely specimen processing is limited. [37] Even so, emerging evidence from high-income settings suggests that IGRAs can be cost-effective when deployed strategically in high-risk populations, where the pre-test probability of LTBI is higher and the downstream benefits of preventive therapy are greater. [37][38] As with TST, IGRA results can be affected by immune status. False-negative results may occur in central nervous system TB or in individuals with impaired immune function, including older adults and persons with innate or acquired interferon-gamma deficiencies. [39][40] These scenarios highlight a crucial interpretive point for laboratory specialists: a negative immune-based assay does not definitively exclude infection in immunocompromised hosts, and clinical context must remain dominant. False-positive IGRA results are uncommon but can occur under specific circumstances, such as specimen contamination with viable TB organisms. [41] Indeterminate IGRA results deserve careful interpretation because they often signal a technical or immunologic problem rather than an intermediate infection state. Indeterminate findings may result from reduced responsiveness in the mitogen control, as occurs with

immunosuppression, or from elevated interferon-gamma levels in negative control tubes, which can be caused by heterophile antibodies, antigen handling errors, or autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis. [22][42] From a public health standpoint, indeterminate results are operationally significant because they can impede decision-making in contact investigations, delay preventive therapy initiation in high-risk individuals, and require repeat testing or alternative approaches.

Use of Immune-Based Tests for Monitoring

TST and IGRA have limited value for monitoring response to TB treatment. Although some decline in IGRA positivity rates may occur after treatment, many individuals remain IGRA-positive even after completing LTBI therapy, reflecting persistent immunologic memory rather than ongoing viable infection. [43][44] Similarly, TST measures delayed-type hypersensitivity to tuberculin and does not function as a marker of treatment response or protective immunity. [30] For laboratory and epidemiology professionals, this limitation is essential to avoid misusing immune tests as "test-of-cure" tools, which could lead to unnecessary repeat treatment or misinterpretation of program effectiveness.

Chest Radiography and Sputum Samples

Because immune-based tests cannot exclude active disease, additional evaluation is often necessary to ensure that a positive TST or IGRA represents LTBI rather than unrecognized active TB. In individuals without TB symptoms, a chest radiograph may be sufficient to reasonably exclude active pulmonary TB, particularly when interpreted alongside clinical assessment. However, any clinical concern or radiographic abnormality should prompt further investigation, either for TB disease or for alternative diagnoses. Many conditions can mimic TB radiographically and clinically, including silicosis, malignancy, sarcoidosis, autoimmune disorders such as rheumatoid arthritis and vasculitis, and a range of infectious etiologies including NTM, *Nocardia*, *Cryptococcus*, *Histoplasma*, and *Aspergillus*. [45][46][47][48][49] For public health programs, this differential is not merely theoretical: misclassifying a non-TB disease as TB can lead to inappropriate isolation, unnecessary contact tracing, and avoidable stigma, whereas missing true TB can perpetuate transmission. When active pulmonary TB is suspected—based on symptoms, radiographic findings, or epidemiologic risk—microbiologic confirmation becomes central. A commonly used approach is the collection and evaluation of three early morning sputum samples for acid-fast staining, mycobacterial culture, and nucleic acid amplification testing. [22] Acid-fast smears provide rapid but imperfect evidence of mycobacteria; culture remains the definitive method for organism recovery and drug susceptibility testing but requires prolonged incubation; NAAT offers more rapid identification of *M. tuberculosis* and, in some platforms, can detect genetic markers of drug resistance. The detection of *M. tuberculosis* in sputum is diagnostic of active TB and has immediate infection-control implications: such patients can transmit disease and typically require isolation according to local protocols. This finding also triggers mandatory public health notification for contact tracing and implementation of measures to limit community transmission. [50] An important nuance for epidemiology and infection control is that infectivity is largely determined by pulmonary involvement with organism access to airways. Patients with isolated extrapulmonary TB manifestations are generally considered noninfectious, though they may still require treatment and public health reporting depending on jurisdiction. [51] This distinction shapes resource allocation and contact investigation strategy, focusing transmission control efforts where they are most likely to yield benefit.

Integrating Findings into a Cohesive Diagnostic Pathway

In practice, evaluation proceeds as an integrated algorithm rather than a single test decision. First, clinicians identify candidates for LTBI testing based on epidemiologic exposure risk and reactivation risk. Second, they perform symptom screening and, when indicated, chest radiography to exclude active disease. Third, they select an immune-based test—TST or IGRA—based on local epidemiology, BCG vaccination history, laboratory capacity, and the patient's immune status. Fourth, if any evidence suggests possible active TB (symptoms, abnormal imaging, high-risk clinical context), microbiologic testing with sputum and molecular methods is pursued promptly, and infection-control and public health notification pathways are initiated as required. Across this continuum, the key conceptual anchor remains constant: LTBI is an immunologic diagnosis made only after active TB has been reasonably excluded, and laboratory results must always be interpreted within a structured clinical and epidemiologic context.

Treatment / Management

The management of latent tuberculosis infection (LTBI) is shaped by the distinctive biology of *Mycobacterium tuberculosis* and the overarching public health objective of preventing progression to active, transmissible disease. Mycobacteria, including *M. tuberculosis*, exhibit intrinsic resistance to many commonly used antibacterial agents, largely because of their lipid-rich cell envelope, slow growth, and specialized metabolic pathways. [52] As a result, effective therapy requires antimycobacterial drugs with activity against these organisms, and the preventive regimens used for LTBI generally rely on one or two such agents rather than the multi-drug combinations required for active disease. [53] This difference reflects both the lower organism burden

typically present during latency and the need to minimize toxicity while still providing sufficient antimicrobial pressure to reduce future reactivation risk. By contrast, the standard regimen for drug-susceptible pulmonary TB disease is substantially more complex, specifically because active disease involves higher bacterial loads, actively replicating organisms, and an increased risk of selecting resistant subpopulations if treatment is inadequate. A conventional approach consists of rifampicin, isoniazid, pyrazinamide, and ethambutol for the initial two months, followed—if susceptibility testing confirms sensitivity to rifampicin and isoniazid—by continuation of those two drugs for an additional four months, with cessation of pyrazinamide and ethambutol. [53][54] This phased strategy is designed to rapidly reduce bacterial burden, limit emergence of resistance, and consolidate cure. Importantly, susceptibility testing that informs active TB regimens cannot be applied in the same way to LTBI management, because latency is not typically associated with culture confirmation of *M. tuberculosis* in the absence of clinical disease; therefore, routine culture-based susceptibility data are not available to guide individualized LTBI therapy. [55]

A particularly challenging management context involves individuals who are close contacts of patients with multidrug-resistant TB (MDR-TB). Epidemiologically, close contacts of MDR-TB cases are more likely to have LTBI due to intense exposure, and close contacts of active TB cases may themselves be more likely to harbor MDR-TB. [56][57] Despite the intuitive appeal of tailoring preventive therapy based on the drug-resistance profile of an index case, the evidence base supporting best practices for managing MDR-TB contacts remains limited. [56] In the absence of strong data demonstrating superior outcomes from selecting LTBI treatment regimens according to the susceptibility patterns of MDR-TB source cases, approaches have often been guided by expert opinion and the clinician's assessment of the individual's probability of having acquired MDR infection, the feasibility of close monitoring, and the balance of potential benefit and harm in the specific clinical context. [58][59] This uncertainty highlights the need for careful clinical judgment and robust public health coordination, particularly when decisions must be made under incomplete microbiologic information. The central goal of LTBI treatment is prevention: reducing the likelihood that a person with immunologic evidence of infection will progress to active disease at some point in the future. Yet preventive therapy is not universally benign, and treatment decisions must acknowledge that most individuals with untreated LTBI will not reactivate over their lifetime. Accordingly, the anticipated benefit—averting active TB, its morbidity, and its transmission potential—must be weighed against the risk of adverse effects from therapy. This trade-off is particularly salient for isoniazid-containing regimens, which are associated with clinically important hepatotoxicity risk in some patients. [60][61] In practice, this means that LTBI treatment is not merely a protocol-driven exercise, but a risk–benefit decision that incorporates patient-specific factors such as age, comorbidities, concurrent medications, and the presence of immunosuppression or other reactivation risks.

To support this individualized decision-making, several clinical calculators have been developed to estimate three interrelated quantities: the probability that a positive test represents true infection, the patient's predicted risk of reactivation, and the likelihood of serious hepatotoxicity if LTBI therapy is initiated. [62][63] Although such tools do not replace clinical judgment, they provide a structured way to synthesize epidemiologic and clinical variables, especially in settings where the pre-test probability of infection varies widely across subpopulations. For laboratory specialists and public health professionals, these tools also underscore an important principle: test results acquire meaning only in context, and optimizing outcomes requires integrating diagnostics with risk stratification and medication safety considerations. The most commonly used LTBI regimens generally fall into three broad categories. One approach is rifampicin monotherapy administered daily for approximately three to four months. [53] A second approach is combination therapy using rifampicin or rifapentine plus isoniazid for approximately three to four months. [53] A third option is isoniazid monotherapy administered daily for six to nine months. [53] The selection among these regimens is influenced by multiple practical and clinical factors, including medication cost and availability, expected adherence over the course of therapy, anticipated efficacy, and the adverse-effect profile—particularly hepatotoxicity risk. Shorter regimens may offer adherence advantages for some patients and programs, while longer regimens may be preferred in specific circumstances based on local practice patterns, contraindications, or drug interactions.

Understanding the pharmacologic basis of these regimens helps clarify their risk–benefit characteristics. Isoniazid is a cornerstone antimycobacterial agent that inhibits synthesis of mycolic acids, essential structural components of the mycobacterial cell envelope. [64] This mechanism explains its specificity for mycobacteria and its value in both preventive and active TB regimens. Isoniazid is often less expensive than rifamycin-based alternatives, which can be relevant for large-scale public health programs; however, it is associated with a higher risk of adverse effects in some populations, contributing to the clinical emphasis on hepatotoxicity screening, counseling, and monitoring.

Rifamycins, by contrast, inhibit bacterial DNA-dependent RNA polymerase and have activity against a broad range of organisms, including mycobacteria. [65] Within LTBI treatment, rifampicin and rifapentine are particularly useful agents, with rifapentine offering the practical advantage of a longer half-life that enables weekly dosing in certain regimens. [66] These pharmacologic properties can improve feasibility and adherence in selected patients, though rifamycin use also requires careful attention to drug–drug interactions and contraindications in specific clinical settings. From an outcomes perspective, established LTBI regimens are associated with substantial protective benefit. Reported protective efficacy ranges from approximately 60% to 90%, with evidence of durability extending for as long as 19 years in some analyses. [67] This long-term protection is a core justification for investing in LTBI programs, particularly in low-incidence countries where preventing reactivation has outsized impact on progress toward elimination targets. Nevertheless, efficacy is not uniform across all contexts. In persons living with HIV in high-incidence settings, the optimal duration of LTBI therapy remains less clearly defined. [68][69] This uncertainty reflects the complex interplay of repeated or ongoing exposure risk, evolving immune status, and the possibility that reinfection may occur even after completion of preventive therapy. In such environments, decisions regarding preventive strategies may require closer linkage between individual clinical management and broader epidemiologic interventions, including infection control, contact tracing, and community-level transmission reduction. In sum, LTBI treatment is best understood as a preventive intervention that must reconcile microbiologic constraints, diagnostic uncertainty, and patient-centered safety considerations. Because latent infection cannot be managed using culture-based susceptibility guidance in routine practice, [55] regimen selection relies on established protocols, assessment of MDR exposure context when relevant, [56][57][58][59] and an explicit evaluation of the likelihood of benefit versus potential harms—especially hepatotoxicity in isoniazid-based strategies. [60][61] When implemented thoughtfully, modern LTBI regimens offer meaningful and durable reduction in progression to active disease, [67] supporting both individual health and population-level TB control.

Differential Diagnosis

The differential diagnosis of latent tuberculosis infection (LTBI) is inherently shaped by the fact that LTBI is not a clinical syndrome but an inferred state of infection detected through screening. Patients with LTBI are asymptomatic by definition and typically come to attention because of occupational, immigration, contact-tracing, or medical risk–based testing strategies. As a result, the principal diagnostic challenge is not distinguishing LTBI from other symptomatic conditions that "look like" TB, but rather interpreting immune-based test results in a manner that accurately separates latent infection from active disease, previously resolved infection, vaccination-related cross-reactivity, and immunologic false positives or negatives. No single test is sufficient to establish LTBI in isolation; diagnosis requires a careful synthesis of clinical evaluation, radiographic assessment, and appropriate interpretation of immunologic testing. The most relevant competing diagnoses include active TB disease, previously treated or cleared TB infection, and nontuberculous mycobacterial (NTM) exposures or infections that can generate falsely positive immune-based results—particularly for the tuberculin skin test (TST). [34]

Active Tuberculosis Disease

The most important and immediate differential diagnosis is active TB disease, because missing active disease has direct consequences for patient outcomes and community transmission. From a public health perspective, the central question is not simply whether the patient has been infected, but whether they are currently contagious or have ongoing pathologic disease that requires full multi-drug therapy and isolation protocols. A minimum requirement for excluding active pulmonary TB is that the patient is asymptomatic for TB disease and has a normal chest radiograph. [70] This standard reflects the pragmatic understanding that immune-based tests cannot discriminate active from latent infection and that a radiographically normal chest in an asymptomatic individual substantially reduces the probability of active pulmonary disease. However, exclusion of active TB must be more rigorous when uncertainty persists. Clinical uncertainty may arise from high-risk exposure history, immunosuppression (which can blunt symptoms and distort radiographic findings), abnormal radiographic features that are nonspecific, or the presence of systemic features that are subtle or intermittently reported. In such cases, microbiologic evaluation should be considered. Obtaining three early morning sputum samples for acid-fast staining, mycobacterial culture, and nucleic acid amplification testing provides a structured approach to identifying *M. tuberculosis* in respiratory secretions, thereby confirming active pulmonary infection when positive and supporting isolation and notification pathways. Moreover, clinicians must remain attentive to extrapulmonary TB, which may present without prominent respiratory symptoms. Signs or symptoms suggestive of extrapulmonary involvement—such as lymphadenopathy, meningitic symptoms, persistent focal bone pain, abdominal distension, or serositis—may necessitate targeted imaging, tissue biopsy for histopathology and mycobacterial testing, and, in cases of suspected meningeal TB, lumbar puncture. The key principle is that LTBI should not be diagnosed until active TB has been reasonably excluded, and the threshold for

additional testing should be lower in high-risk individuals where consequences of missed disease are substantial.

Resolved Tuberculosis Infection

A second major differential diagnosis is resolved TB infection, which includes individuals who have either received prior treatment for TB disease or cleared infection naturally but retain immunologic evidence of exposure. These patients may present with a positive TST or IGRA despite absence of current disease, and the immunologic signal may persist for years, reflecting immune memory rather than ongoing viable infection. In this context, the diagnosis of LTBI is complicated by uncertainty about whether viable organisms remain and whether preventive therapy will provide meaningful incremental benefit. Accurate classification requires a detailed history focused on prior exposures, prior TB testing, documented treatment regimens, adherence, and treatment completion, as well as any historical radiographic findings suggestive of prior disease. Establishing a timeframe of exposure and treatment is clinically important because recent infection carries higher reactivation risk than remote infection, and previously treated disease may alter both baseline risk and the interpretation of benefits from preventive therapy. Because the decision to treat LTBI is inherently a risk–benefit assessment, the possibility of resolved infection emphasizes individualized decision-making rather than reflex treatment based solely on test positivity. Clinical calculators may assist clinicians by estimating the likelihood that the test result represents true infection and by quantifying predicted reactivation risk and treatment-related adverse event risk, thereby supporting transparent shared decision-making. [62][63] In practice, this approach aligns clinical management with patient-specific factors and improves consistency in settings where the epidemiologic context varies widely.

Bacille Calmette–Guérin Vaccination

BCG vaccination represents another critical source of diagnostic ambiguity, particularly when TST is used. The TST is not specific for *M. tuberculosis*, and false-positive results can occur in individuals vaccinated with BCG, which is derived from *Mycobacterium bovis*. [34] The magnitude and persistence of BCG-related TST reactivity can vary according to vaccine strain, timing of vaccination (infancy versus later), and booster exposures. In many programmatic settings, this limitation is a major reason to prefer IGRAs, which use antigens absent from BCG and therefore better distinguish true *M. tuberculosis* sensitization from vaccine-induced reactivity. Nevertheless, when TST is the available tool, vaccination history must be carefully elicited, documented, and incorporated into interpretation, especially in low-incidence settings where the pre-test probability of LTBI may be low and the consequences of false-positive classification include unnecessary treatment exposure.

Nontuberculous Mycobacterial Exposure or Infection

Environmental exposure to NTM can also produce false-positive TST results because of antigenic cross-reactivity between some NTM species and PPD tuberculin. NTMs implicated in such cross-reactivity include *M. avium-intracellulare* complex, *M. simiae*, *M. scrofulaceum*, and *M. kansasii*. [31][32] This differential diagnosis is important for laboratory specialists because NTM exposure is geographically variable, influenced by environmental reservoirs such as water and soil, and may be more prevalent in certain communities or occupational contexts. Clinically significant NTM pulmonary disease—particularly due to *M. kansasii* and *M. avium-intracellulare* complex—can occur, especially in individuals with underlying structural lung disease, and may prompt evaluation that initially resembles TB investigations. While IGRAs generally reduce the likelihood of NTM-related false positives because their target antigens are not found in most NTMs, cross-reactivity is not completely impossible across all species, and test interpretation should still account for local epidemiology and clinical context. In summary, the differential diagnosis of LTBI is less about competing symptomatic syndromes and more about accurate classification of infection state and risk. Active TB must be excluded with symptom assessment and chest radiography at minimum, with microbiologic testing and targeted extrapulmonary evaluation when uncertainty remains. [70] Positive immune tests may reflect resolved infection or prior treatment, requiring careful historical reconstruction and individualized risk–benefit analysis supported, when appropriate, by clinical calculators. [62][63] Finally, BCG vaccination and NTM exposures remain critical considerations—particularly for TST interpretation—because they can drive false-positive results and lead to unnecessary therapy if not recognized. [34][31][32]

Pertinent Studies and Ongoing Trials

A persistent scientific and programmatic barrier in latent tuberculosis infection (LTBI) control is the absence of a definitive diagnostic standard that can reliably confirm viable *Mycobacterium tuberculosis* persistence and, crucially, distinguish latent infection from active disease or immunologic scarring after clearance. Current screening tools—most prominently the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—operate by detecting host cellular immune recognition of mycobacterial antigens rather than demonstrating living organisms. This reliance on immunologic memory creates an intrinsic interpretive limitation: a positive result indicates prior sensitization but does not specify whether bacilli remain viable, whether the infection has been sterilized by the host, or whether

disease is currently active. The problem is particularly evident for the TST, which may yield positive results in individuals who have cleared infection as well as in patients with active pulmonary TB, thereby eroding its discriminative value when used in isolation and complicating clinical decision-making in settings where pre-test probability varies widely. [71] Accordingly, a major focus of contemporary research is the development of next-generation diagnostics that go beyond exposure detection and instead aim to characterize infection state and progression risk. Investigational approaches include immunodiagnostic biomarkers designed to better differentiate latent infection from active disease by capturing qualitative differences in immune activation, effector function, or inflammatory signaling that are not represented by binary "positive/negative" measures of T-cell sensitization. This research agenda reflects the recognition that "latent" and "active" TB are better understood as points on a biological spectrum rather than strictly discrete categories, and therefore biomarkers that quantify immune phenotypes, cytokine signatures, or cellular transcriptional profiles may provide improved resolution of infection states. [32] Ongoing trials in this area commonly evaluate candidate biomarkers in longitudinal cohorts, seeking to determine whether particular immune signatures predict imminent progression, treatment responsiveness, or sustained sterilization after preventive therapy. In parallel, studies also examine how immunosuppression, age, coinfections, and prior BCG vaccination influence biomarker performance, since these factors can distort conventional immune testing and contribute to indeterminate or misleading results. The public health relevance of these investigations is substantial: more accurate diagnostics could reduce unnecessary preventive treatment in individuals unlikely to benefit, concentrate resources on those at highest risk of reactivation, and improve program efficiency by limiting overtreatment driven by nonspecific test positivity. Ultimately, progress in LTBI management will depend not only on better drugs and shorter regimens, but also on diagnostic innovations that can move the field from "evidence of exposure" toward "evidence of clinically meaningful persistent infection and risk," thereby enabling more precise, safer, and more cost-effective prevention strategies.

Toxicity and Adverse Effect Management

The safety profile of latent tuberculosis infection (LTBI) therapy is a central determinant of whether preventive treatment is justified and whether it can be delivered successfully at scale. The most clinically consequential adverse event is drug-induced hepatitis, which can range from asymptomatic transaminase elevation to severe acute liver injury requiring hospitalization, though fatal outcomes are uncommon. [72][73] Hepatotoxicity is most frequently associated with regimens containing isoniazid, but clinically meaningful liver injury can also occur with rifamycin-based regimens, underscoring that hepatic monitoring is relevant across treatment options. [74] Risk stratification before treatment initiation is therefore essential. Recognized risk factors for serious hepatotoxicity include elevated baseline transaminase levels, pre-existing liver disease, hypoalbuminemia, increasing age, antiretroviral therapy exposure, HIV infection, hepatitis B surface antigen seropositivity, alcohol use disorder, concurrent use of other hepatotoxic medications, and pregnancy. [72][73][75][76][77][78][79] Reports indicating higher hepatotoxicity rates among Indian patients compared with other populations introduce additional complexity; the mechanism is not well understood, emphasizing the need for careful monitoring and contextual awareness when applying risk predictions across diverse populations. [80] Pediatric safety considerations are also important: children across ethnicities have been described as experiencing higher incidences of hepatotoxicity compared with adults, reinforcing the need for age-appropriate monitoring strategies and vigilant clinical follow-up. For patients with elevated risk, baseline liver function testing before initiating therapy is recommended, with repeat assessment at least monthly until completion of treatment. [81] Monitoring, however, should not be restricted to laboratory surveillance alone. Patient-centered adverse effect management requires education regarding early symptoms of hepatitis, including anorexia, nausea, vomiting, abdominal pain (particularly right upper quadrant discomfort), jaundice, dark urine, and unexplained fatigue. Explicit instructions to seek early evaluation if symptoms develop is a key safety intervention, particularly in programs serving populations with limited healthcare access or competing priorities. Timely recognition can allow regimen interruption and supportive management before progression to severe liver injury.

Beyond hepatotoxicity, isoniazid can induce peripheral neuropathy through functional vitamin B6 deficiency, a complication that is preventable yet often underrecognized in routine counseling. [82] Pyridoxine supplementation is not universally required, but it should be prescribed for individuals at higher risk of neuropathy, including those who are pregnant, living with HIV, affected by diabetes, malnutrition, alcohol misuse, chronic kidney disease, or advanced age. [83][84] This targeted approach reflects a balance between preventing morbidity and avoiding unnecessary supplementation in low-risk individuals. Rifamycin-related adverse effects require distinct anticipatory guidance and monitoring. Common and benign effects include orange-red discoloration of urine, tears, and other body fluids; although harmless, this can cause alarm if not preemptively explained. More clinically significant adverse effects include hypersensitivity reactions,

renal impairment, hemolytic anemia, and thrombocytopenic purpura. [85][86][73] Drug–drug interactions are particularly prominent with rifamycins because of effects on hepatic metabolic pathways; thus, a comprehensive medication reconciliation is indispensable before initiation. Anticoagulants such as warfarin, apixaban, and rivaroxaban warrant special caution and may represent relative contraindications due to clinically significant cytochrome P450–mediated interactions that can compromise anticoagulation control and patient safety. [87] In practice, this interaction profile reinforces the value of pharmacist involvement, protocolized screening for interacting medications, and rapid pathways to modify regimens when interactions cannot be mitigated.

Prognosis

The prognosis of LTBI management should be understood in preventive terms: treatment aims to eliminate or suppress viable mycobacteria before the development of active TB disease, thereby reducing individual morbidity and interrupting potential future transmission chains. The protective efficacy of established LTBI regimens is substantial, commonly reported in the range of 60% to 90%, indicating meaningful risk reduction across diverse settings and follow-up periods. [88][89] In contrast, without treatment, approximately 5% to 15% of individuals with LTBI will reactivate at some point during their lifetime, though risk is concentrated in the early years after infection and is amplified by immunosuppression and other host vulnerabilities. [20] Despite clear aggregate risk estimates, prognosis remains difficult to individualize. Host, pathogen, and environmental determinants of progression are increasingly well described—ranging from immunosuppressive therapies and HIV infection to bacterial lineage variation—yet it remains impossible to predict with certainty which infected individuals will progress to active disease. [9][21] This uncertainty creates a fundamental ethical and clinical tension in LTBI programs: many treated individuals would not have reactivated even without therapy. In practical terms, this means that a large proportion of people receiving LTBI treatment experience medication exposure and potential adverse effects without direct clinical benefit, even though population-level benefit is achieved through prevention of cases that would have occurred. This reality does not invalidate LTBI treatment; rather, it underscores the need for careful candidate selection, transparent counseling, and structured monitoring that maximizes benefit while minimizing avoidable harm. Risk calculators and targeted testing strategies are therefore not ancillary tools but core components of responsible preventive care, ensuring that treatment is preferentially directed toward those most likely to benefit and least likely to experience severe toxicity.

Complications

Complications of LTBI treatment are best conceptualized as preventable harms arising from therapy rather than from latent infection itself, given that LTBI is asymptomatic. The dominant complication risk is treatment-related toxicity, particularly hepatotoxicity, which is why structured monitoring is a central element of safe program design. Regular clinic follow-up or case management visits are not merely administrative; they function as an active surveillance system for adverse effects, with liver function monitoring prioritized for individuals at increased risk. [81] This approach supports early detection of subclinical injury, timely modification or cessation of therapy, and prevention of escalation to severe hepatic events. A longstanding concern in TB control has been the possibility that widespread LTBI treatment could increase drug resistance by exposing large numbers of individuals to antimycobacterial agents. Current evidence has not validated this concern through comprehensive, systematic meta-analyses, suggesting that resistance amplification attributable to LTBI programs is not a dominant observed outcome under standard practices. [81][90] Nevertheless, the absence of definitive proof of harm should not be interpreted as justification for complacency. Surveillance systems that monitor drug resistance trends remain essential, particularly because resistance dynamics may change with evolving prescribing patterns, variable adherence, and shifting epidemiology. [91] In well-functioning TB programs, resistance surveillance complements toxicity monitoring: one protects the individual patient from treatment harms, while the other protects the population from emergent antimicrobial resistance that could compromise future TB control efforts.

Patient Education

Medication adherence is one of the most influential variables determining LTBI treatment success. Preventive therapy is uniquely vulnerable to nonadherence because patients feel well, may have competing socioeconomic demands, and may perceive limited immediate benefit. Recognizing these barriers, there has been a clear clinical shift toward shorter and less complex regimens, which improve feasibility and can enhance completion rates compared with longer, single-drug strategies. [92] However, regimen selection alone is insufficient. Evidence supports the value of peer support, structured case management, and tailored educational interventions in improving adherence, particularly in vulnerable populations where barriers include unstable housing, limited transportation, stigma, and fragmented healthcare access. [93] Effective education should clarify the nature of LTBI—an infection state with future risk rather than current illness—and explain the rationale for preventive therapy in accessible terms. Patients should

understand that treatment aims to prevent reactivation and protect both individual health and community well-being. Education must also explicitly address adverse effects, with special emphasis on hepatotoxicity risk, early warning symptoms, and clear instructions on when and how to seek care. Counseling should include guidance on alcohol use, concurrent medication disclosure, and the importance of consistent dosing. Importantly, education should be culturally and linguistically appropriate and should acknowledge patient concerns about stigma and confidentiality. When patients understand both the benefits and risks, adherence tends to improve, and early reporting of adverse symptoms becomes more likely, enhancing safety. In this way, patient education functions as both a deterrence strategy against noncompletion and a pharmacovigilance intervention that reduces the likelihood of severe toxicity.

Enhancing Healthcare Team Outcomes

In high-income, low-incidence settings such as the United States, the public health strategy for TB control relies heavily on targeted testing and treatment of individuals at elevated risk of progression or new infection, rather than population-wide screening. [94][95] TB-focused clinics and public health services are pivotal in conducting contact investigations, screening close contacts of active cases, and coordinating preventive therapy. However, many high-risk individuals are first encountered outside specialized TB services. Rheumatology practices, primary care clinics, sexual health services, and programs serving vulnerable populations frequently identify candidates for LTBI testing—especially those starting biologic therapies, those living with HIV, or individuals affected by housing instability—and play a critical referral role for further assessment and treatment. [96][97][98][99] Interprofessional collaboration measurably improves safety and outcomes in LTBI management. Pharmacists contribute essential expertise in selecting appropriate regimens, anticipating and mitigating hepatotoxicity risk, and identifying clinically significant drug–drug interactions—particularly with rifamycin-based therapies, where metabolic induction can compromise the efficacy or safety of concurrent medications. Nurses trained in TB care, cultural health workers, and case managers provide the operational backbone of many LTBI programs by supporting adherence, organizing follow-up visits, monitoring symptoms, and facilitating laboratory testing. Their longitudinal engagement is especially valuable for patients facing social barriers that would otherwise lead to treatment interruption. Social workers further strengthen outcomes by addressing upstream determinants of nonadherence, including transportation limitations, unstable housing, food insecurity, and challenges navigating insurance or immigration-related barriers. A coordinated approach requires shared competence across disciplines in TB screening methods, especially interpretation of TST and IGRA results in the context of BCG vaccination, immunosuppression, and local epidemiology. Effective interprofessional communication—particularly around social determinants, stigma risks, and barriers to completion—supports holistic care and reduces preventable discontinuation. In low-incidence settings, maintaining vigilance despite reduced prevalence is an ongoing challenge; standardized protocols, continuous education, simulation of contact investigation workflows, and patient-centered ethical practices help sustain program quality. Ultimately, successful LTBI screening and treatment depend not only on the right drugs, but on integrated systems that combine accurate risk stratification, proactive toxicity management, adherence support, and coordinated public health–clinical partnerships to achieve durable prevention outcomes.

Conclusion:

LTBI represents a silent yet significant threat to global TB elimination efforts. While immune-based tests provide practical tools for identifying infection, their inability to confirm viability or exclude active disease underscores the necessity of comprehensive evaluation incorporating symptom screening and radiographic assessment. Preventive therapy remains a cornerstone of TB control, offering substantial protection against progression; however, its implementation must balance anticipated benefit with potential harm, particularly hepatotoxicity. Individualized decision-making—guided by risk stratification, clinical calculators, and structured monitoring—ensures that therapy is directed toward those most likely to benefit. Programmatic success depends on more than pharmacology. Patient education, adherence support, and culturally sensitive counseling are critical to overcoming barriers inherent in treating asymptomatic individuals. Interprofessional collaboration among clinicians, pharmacists, nurses, and public health teams strengthens safety and continuity of care, while emerging research on biomarkers and shorter regimens promises to refine diagnostic precision and improve completion rates. Ultimately, LTBI management is a preventive intervention with profound population-level impact, requiring integration of laboratory science, clinical judgment, and public health ethics to achieve durable reductions in TB incidence and advance toward global elimination goals.

References:

1. Nissapatorn V, Kuppusamy I, Anuar AK, Quek KF, Latt HM. Tuberculosis: clinical manifestations and outcomes. The Southeast Asian journal of tropical medicine and public health. 2003:34 Suppl 2():147-52
2. Munteanu I, Cioran N, van Hest R, Abubakar I, Story A, Chiotan D, de Vries G, Mahler B. Tuberculosis Surveillance in

Romania Among Vulnerable Risk Groups Between 2015 and 2017. Therapeutics and clinical risk management. 2022:18():439-446. doi: 10.2147/TCRM.S347748.

3. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014 Jun:43(6):1763-75. doi: 10.1183/09031936.00193413.
4. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, Den Boon S, Borroto Gutierrez SM, Bruchfeld J, Burhan E, Cavalcante S, Cedillos R, Chaisson R, Chee CB, Chesire L, Corbett E, Dara M, Denholm J, de Vries G, Falzon D, Ford N, Gale-Rowe M, Gilpin C, Girardi E, Go UY, Govindasamy D, D Grant A, Grzemska M, Harris R, Horsburgh CR Jr, Ismayilov A, Jaramillo E, Kik S, Kranzer K, Lienhardt C, LoBue P, Lönnroth K, Marks G, Menzies D, Migliori GB, Mosca D, Mukadi YD, Mwinga A, Nelson L, Nishikiori N, Oordt-Speets A, Rangaka MX, Reis A, Rotz L, Sandgren A, Sañé Schepisi M, Schünemann HJ, Sharma SK, Sotgiu G, Stagg HR, Sterling TR, Tayeb T, Uplekar M, van der Werf MJ, Vandevelde W, van Kessel F, van't Hoog A, Varma JK, Vezhnina N, Voniatis C, Vonk Noordegraaf-Schouten M, Weil D, Weyer K, Wilkinson RJ, Yoshiyama T, Zellweger JP, Raviglione M. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. The European respiratory journal. 2015 Dec:46(6):1563-76. doi: 10.1183/13993003.01245-2015.
5. PaweŁczyk J, Kremer L. The Molecular Genetics of Mycolic Acid Biosynthesis. Microbiology spectrum. 2014 Aug:2(4):MGM2-0003-2013. doi: 10.1128/microbiolspec.MGM2-0003-2013.
6. Gizaw N, Abera A, Sisay S, Desta K, Kreibich S, Gerwing-Adima L, Gebre-Selassie S. The yield of Auramine O staining using led microscopy with bleach treated sputum samples for detection of pulmonary tuberculosis at St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia. Journal of clinical tuberculosis and other mycobacterial diseases. 2020 Feb:18():100140. doi: 10.1016/j.jctube.2019.100140.
7. Kumar M, Kumar G, Kumar R, Muni S, Choubey S, Kumar S, Kumari N. A Comparative Analysis of Microscopy, Culture, and the Xpert Mycobacterium tuberculosis/Rifampicin Assay in Diagnosing Pulmonary Tuberculosis in Human Immunodeficiency-Positive Individuals. Cureus. 2023 Aug:15(8):e42962. doi: 10.7759/cureus.42962.
8. Vongthilath-Moeung R, Poncet A, Renzi G, Schrenzel J, Janssens JP. Time to Detection of Growth for Mycobacterium tuberculosis in a Low Incidence Area. Frontiers in cellular and infection microbiology. 2021:11():704169. doi: 10.3389/fcimb.2021.704169.
9. Chen Y, Liu J, Zhang Q, Wang Q, Chai L, Chen H, Li D, Qiu Y, Wang Y, Shen N, Wang J, Xie X, Li S, Li M. Epidemiological features and temporal trends of HIV-negative tuberculosis burden from 1990 to 2019: a retrospective analysis based on the Global Burden of Disease Study 2019. BMJ open. 2023 Sep 28:13(9):e074134. doi: 10.1136/bmjopen-2023-074134.
10. Jiménez-Corona ME, García-García L, DeRiemer K, Ferreyra-Reyes L, Bobadilla-del-Valle M, Cano-Arellano B, Canizales-Quintero S, Martínez-Gamboa A, Small PM, Sifuentes-Osornio J, Ponce-de-León A. Gender differentials of pulmonary tuberculosis transmission and reactivation in an endemic area. Thorax. 2006 Apr:61(4):348-53
11. Gao J, Zheng P, Fu H. Prevalence of TB/HIV co-infection in countries except China: a systematic review and meta-analysis. PloS one. 2013:8(5):e64915. doi: 10.1371/journal.pone.0064915.
12. Trinh QM, Nguyen HL, Nguyen VN, Nguyen TV, Sintchenko V, Marais BJ. Tuberculosis and HIV co-infection-focus on the Asia-Pacific region. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2015 Mar:32():170-8. doi: 10.1016/j.ijid.2014.11.023.
13. Aabye MG, Ravn P, PrayGod G, Jeremiah K, Mugomela A, Jepsen M, Faurholt D, Range N, Friis H, Changalucha J, Andersen AB. The impact of HIV infection and CD4 cell count on the performance of an interferon gamma release assay in patients with pulmonary tuberculosis. PloS one. 2009:4(1):e4220. doi: 10.1371/journal.pone.0004220.
14. Lin PL, Flynn JL. Understanding latent tuberculosis: a moving target. Journal of immunology (Baltimore, Md. : 1950). 2010 Jul 1:185(1):15-22. doi: 10.4049/jimmunol.0903856.
15. Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis.

BMJ (Clinical research ed.). 2018 Aug 23:362():k2738. doi: 10.1136/bmj.k2738.
16. Huang L, Nazarova EV, Russell DG. Mycobacterium tuberculosis: Bacterial Fitness within the Host Macrophage. Microbiology spectrum. 2019 Mar:7(2):. doi: 10.1128/microbiolspec.BAI-0001-2019.
17. Ehrt S, Schnappinger D, Rhee KY. Metabolic principles of persistence and pathogenicity in Mycobacterium tuberculosis. Nature reviews. Microbiology. 2018 Aug:16(8):496-507. doi: 10.1038/s41579-018-0013-4.
18. Pavlinac PB, Lokken EM, Walson JL, Richardson BA, Crump JA, John-Stewart GC. Mycobacterium tuberculosis bacteremia in adults and children: a systematic review and meta-analysis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2016 Jul:20(7):895-902. doi: 10.5588/ijtld.15.0773.
19. Kiazyk S, Ball TB. Latent tuberculosis infection: An overview. Canada communicable disease report = Releve des maladies transmissibles au Canada. 2017 Mar 2:43(3-4):62-66
20. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. American journal of epidemiology. 1974 Feb:99(2):131-8
21. Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerging microbes & infections. 2016 Feb 3:5(2):e10. doi: 10.1038/emi.2016.10.
22. Loddenkemper R, Lipman M, Zumla A. Clinical Aspects of Adult Tuberculosis. Cold Spring Harbor perspectives in medicine. 2015 Feb 6:6(1):a017848. doi: 10.1101/cshperspect.a017848.
23. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulmonary medicine. 2013:2013():828939. doi: 10.1155/2013/828939.
24. Iossifova Y, Bailey R, Wood J, Kreiss K. Concurrent silicosis and pulmonary mycosis at death. Emerging infectious diseases. 2010 Feb:16(2):318-20. doi: 10.3201/eid1602.090824.
25. Hermansen T, Lillebaek T, Hansen AB, Andersen PH, Ravn P. QuantiFERON–TB Gold In-Tube test performance in Denmark. Tuberculosis (Edinburgh, Scotland). 2014 Dec:94(6):616-21
26. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Annals of internal medicine. 2007 Mar 6:146(5):340-54
27. Pollock L, Basu Roy R, Kampmann B. How to use: interferon γ release assays for tuberculosis. Archives of disease in childhood. Education and practice edition. 2013 Jun:98(3):99-105. doi: 10.1136/archdischild-2013-303641.
28. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1993 Dec:17(6):968-75
29. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet. Infectious diseases. 2008 Jun:8(6):359-68. doi: 10.1016/S1473-3099(08)70071-9.
30. Nayak S, Acharjya B. Mantoux test and its interpretation. Indian dermatology online journal. 2012 Jan:3(1):2-6. doi: 10.4103/2229-5178.93479.
31. Haimi-Cohen Y, Zeharia A, Mimouni M, Soukhman M, Amir J. Skin indurations in response to tuberculin testing in patients with nontuberculous mycobacterial lymphadenitis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2001 Nov 15:33(10):1786-8
32. Lindeboom JA, Kuijper EJ, Prins JM, Bruijnesteijn van Coppenraet ES, Lindeboom R. Tuberculin skin testing is useful in the screening for nontuberculous mycobacterial cervicofacial lymphadenitis in children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006 Dec 15:43(12):1547-51
33. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2006 Nov:10(11):1192-204
34. Pai M, Behr M. Latent Mycobacterium tuberculosis Infection and Interferon-Gamma Release Assays. Microbiology spectrum. 2016 Oct:4(5):. doi: 10.1128/microbiolspec.TBTB2-0023-2016.
35. Yang C, Luo X, Fan L, Sha W, Xiao H, Cui H. Performance of Interferon-Gamma Release Assays in the Diagnosis of

Nontuberculous Mycobacterial Diseases-A Retrospective Survey From 2011 to 2019. Frontiers in cellular and infection microbiology. 2020:10():571230. doi: 10.3389/fcimb.2020.571230.

36. Augustynowicz-Kopeć E, Siemion-Szcześniak I, Zabost A, Wyrostkiewicz D, Filipczak D, Oniszh K, Gawryluk D, Radzikowska E, Korzybski D, Szturmowicz M. Interferon Gamma Release Assays in Patients with Respiratory Isolates of Non-Tuberculous Mycobacteria - a Preliminary Study. Polish journal of microbiology. 2019:68(1):15-19. doi: 10.21307/pjm-2019-002.
37. Nienhaus A, Schablon A, Costa JT, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC health services research. 2011 Sep 30:11():247. doi: 10.1186/1472-6963-11-247.
38. Mahon J, Beale S, Holmes H, Arber M, Nikolayevskyy V, Alagna R, Manissero D, Dowdy D, Migliori GB, Sotgiu G, Duarte R. A systematic review of cost-utility analyses of screening methods in latent tuberculosis infection in high-risk populations. BMC pulmonary medicine. 2022 Oct 5:22(1):375. doi: 10.1186/s12890-022-02149-x.
39. Nguyen DT, Teeter LD, Graves J, Graviss EA. Characteristics Associated with Negative Interferon-γ Release Assay Results in Culture-Confirmed Tuberculosis Patients, Texas, USA, 2013-2015. Emerging infectious diseases. 2018 Mar:24(3):534-540. doi: 10.3201/eid2403.171633.
40. Yamasue M, Komiya K, Usagawa Y, Umeki K, Nureki SI, Ando M, Hiramatsu K, Nagai H, Kadota JI. Factors associated with false negative interferon-γ release assay results in patients with tuberculosis: A systematic review with meta-analysis. Scientific reports. 2020 Jan 31:10(1):1607. doi: 10.1038/s41598-020-58459-9.
41. Slater M, Parsonnet J, Banaei N. Investigation of false-positive results given by the QuantiFERON-TB Gold In-Tube assay. Journal of clinical microbiology. 2012 Sep:50(9):3105-7. doi: 10.1128/JCM.00730-12.
42. Powell RD 3rd, Whitworth WC, Bernardo J, Moonan PK, Mazurek GH. Unusual interferon gamma measurements with QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube tests. PloS one. 2011:6(6):e20061. doi: 10.1371/journal.pone.0020061.
43. Chee CB, KhinMar KW, Gan SH, Barkham TM, Koh CK, Shen L, Wang YT. Tuberculosis treatment effect on T-cell interferon-gamma responses to Mycobacterium tuberculosis-specific antigens. The European respiratory journal. 2010 Aug:36(2):355-61. doi: 10.1183/09031936.00151309.
44. Dyrhol-Riise AM, Gran G, Wentzel-Larsen T, Blomberg B, Haanshuus CG, Mørkve O. Diagnosis and follow-up of treatment of latent tuberculosis; the utility of the QuantiFERON-TB Gold In-tube assay in outpatients from a tuberculosis low-endemic country. BMC infectious diseases. 2010 Mar 8:10():57. doi: 10.1186/1471-2334-10-57.
45. Wong B, Tan E, McLean-Tooke A. Pulmonary granulomas in a patient with positive ANCA and history of tuberculosis: case report. BMC pulmonary medicine. 2020 Aug 14:20(1):219. doi: 10.1186/s12890-020-01258-9.
46. Gupta D, Agarwal R, Aggarwal AN, Jindal SK. Sarcoidosis and tuberculosis: the same disease with different manifestations or similar manifestations of different disorders. Current opinion in pulmonary medicine. 2012 Sep:18(5):506-16. doi: 10.1097/MCP.0b013e3283560809.
47. Banner AS. Tuberculosis. Clinical aspects and diagnosis. Archives of internal medicine. 1979 Dec:139(12):1387-90
48. Saavedra FT, Sierra LL, Zuluaica AM, Botero EC. Diagnosing Caplan syndrome in a patient with silicosis and rheumatoid arthritis: imaging shows miliary pattern and cavity lung lesions. Lancet (London, England). 2023 Jun 24:401(10394):2148. doi: 10.1016/S0140-6736(23)01090-5.
49. Nakatudde I, Kasirye P, Kiguli S, Musoke P. It is not always Tuberculosis! A case of pulmonary cryptococcosis in an immunocompetent child in Uganda. African health sciences. 2021 Sep:21(3):990-994. doi: 10.4314/ahs.v21i3.5.
50. Kasaie P, Andrews JR, Kelton WD, Dowdy DW. Timing of tuberculosis transmission and the impact of household contact tracing. An agent-based simulation model. American journal of respiratory and critical care medicine. 2014 Apr 1:189(7):845-52. doi: 10.1164/rccm.201310-1846OC.
51. Chaw L, Mat Salleh L, Abdul Hamid R, Thu K. Epidemiology of extrapulmonary tuberculosis in Brunei Darussalam: a retrospective cohort study. BMJ open. 2023 Aug 23:13(8):e073266. doi: 10.1136/bmjopen-2023-073266.
52. Gygli SM, Borrell S, Trauner A, Gagneux S. Antimicrobial resistance in Mycobacterium tuberculosis: mechanistic and evolutionary

perspectives. FEMS microbiology reviews. 2017 May 1:41(3):354-373. doi: 10.1093/femsre/fux011.

53. Huaman MA, Sterling TR. Treatment of Latent Tuberculosis Infection-An Update. Clinics in chest medicine. 2019 Dec:40(4):839-848. doi: 10.1016/j.ccm.2019.07.008.
54. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM, Ho CS, Hopewell PC, Keshavjee SA, Lienhardt C, Menzies R, Merrifield C, Narita M, O'Brien R, Peloquin CA, Raftery A, Saukkonen J, Schaaf HS, Sotgiu G, Starke JR, Migliori GB, Vernon A. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016 Oct 1:63(7):853-67. doi: 10.1093/cid/ciw566.
55. Heyckendorf J, Gillespie SH, Ruhwald M. Culture-free proof of Mycobacterium tuberculosis - a new assay for viable bacteria. EBioMedicine. 2020 Dec:62():103117. doi: 10.1016/j.ebiom.2020.103117.
56. Chang V, Ling RH, Velen K, Fox GJ. Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia. ERJ open research. 2021 Jul:7(3):. pii: 00149-2021. doi: 10.1183/23120541.00149-2021.
57. Kritski AL, Marques MJ, Rabahi MF, Vieira MA, Werneck-Barroso E, Carvalho CE, Andrade Gde N, Bravo-de-Souza R, Andrade LM, Gontijo PP, Riley LW. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. American journal of respiratory and critical care medicine. 1996 Jan:153(1):331-5
58. van der Werf MJ, Sandgren A, Manissero D. Management of contacts of multidrug-resistant tuberculosis patients in the European Union and European Economic Area. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012:16(3):426. doi: 10.5588/ijtld.11.0605.
59. Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2017 Mar:23(3):147-153. doi: 10.1016/j.cmi.2016.08.024.
60. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999 Mar 17:281(11):1014-8
61. Ngongondo M, Miyahara S, Hughes MD, Sun X, Bisson GP, Gupta A, Kumwenda J, Lavenberg JA, Torres TS, Nyirenda M, Kidonge KK, Hosseinipour MC, AIDS Clinical Trials Group A5274 (REMEMBER) Study Team. Hepatotoxicity During Isoniazid Preventive Therapy and Antiretroviral Therapy in People Living With HIV With Severe Immunosuppression: A Secondary Analysis of a Multi-Country Open-Label Randomized Controlled Clinical Trial. Journal of acquired immune deficiency syndromes (1999). 2018 May 1:78(1):54-61. doi: 10.1097/QAI.0000000000001641.
62. Puyat JH, Shulha HP, Balshaw R, Campbell JR, Law S, Menzies R, Johnston JC. How Well Does TSTin3D Predict Risk of Active Tuberculosis in the Canadian Immigrant Population? An External Validation Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021 Nov 2:73(9):e3486-e3495. doi: 10.1093/cid/ciaa780.
63. Scolarici M, Dekitani K, Chen L, Sokol-Anderson M, Hoft DF, Chatterjee S. A scoring strategy for progression risk and rates of treatment completion in subjects with latent tuberculosis. PloS one. 2018:13(11):e0207582. doi: 10.1371/journal.pone.0207582.
64. Timmins GS, Deretic V. Mechanisms of action of isoniazid. Molecular microbiology. 2006 Dec:62(5):1220-7
65. Wehrli W. Rifampin: mechanisms of action and resistance. Reviews of infectious diseases. 1983 Jul-Aug:5 Suppl 3():S407-11
66. Zheng C, Hu X, Zhao L, Hu M, Gao F. Clinical and pharmacological hallmarks of rifapentine's use in diabetes patients with active and latent tuberculosis: do we know enough? Drug design, development and therapy. 2017:11():2957-2968. doi: 10.2147/DDDT.S146506.
67. Lobue P, Menzies D. Treatment of latent tuberculosis infection: An update. Respirology (Carlton, Vic.). 2010

May:15(4):603-22. doi: 10.1111/j.1440-1843.2010.01751.x.
68. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Annals of internal medicine. 2017 Aug 15:167(4):248-255. doi: 10.7326/M17-0609.
69. Person AK, Sterling TR. Treatment of latent tuberculosis infection in HIV: shorter or longer? Current HIV/AIDS reports. 2012 Sep:9(3):259-66. doi: 10.1007/s11904-012-0120-1.
70. Sia IG, Wieland ML. Current concepts in the management of tuberculosis. Mayo Clinic proceedings. 2011 Apr:86(4):348-61. doi: 10.4065/mcp.2010.0820.
71. Zellweger JP, Sotgiu G, Corradi M, Durando P. The diagnosis of latent tuberculosis infection (LTBI): currently available tests, future developments, and perspectives to eliminate tuberculosis (TB). La Medicina del lavoro. 2020 Jun 26:111(3):170-183. doi: 10.23749/mdl.v111i3.9983.
72. Aouam K, Chaabane A, Loussaïef C, Ben Romdhane F, Boughattas NA, Chakroun M. [Adverse effects of antitubercular drugs: epidemiology, mechanisms, and patient management]. Medecine et maladies infectieuses. 2007 May:37(5):253-61
73. Campbell JR, Trajman A, Cook VJ, Johnston JC, Adjobimey M, Ruslami R, Eisenbeis L, Fregonese F, Valiquette C, Benedetti A, Menzies D. Adverse events in adults with latent tuberculosis infection receiving daily rifampicin or isoniazid: post-hoc safety analysis of two randomised controlled trials. The Lancet. Infectious diseases. 2020 Mar:20(3):318-329. doi: 10.1016/S1473-3099(19)30575-4.
74. Fountain FF, Tolley EA, Jacobs AR, Self TH. Rifampin hepatotoxicity associated with treatment of latent tuberculosis infection. The American journal of the medical sciences. 2009 May:337(5):317-20. doi: 10.1097/MAJ.0b013e31818c0134. E
75. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. The European respiratory journal. 1996 Oct:9(10):2026-30
76. Franks AL, Binkin NJ, Snider DE Jr, Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public health reports (Washington, D.C. : 1974). 1989 Mar-Apr:104(2):151-5
77. Yimer G, Gry M, Amogne W, Makonnen E, Habtewold A, Petros Z, Aderaye G, Schuppe-Koistinen I, Lindquist L, Aklillu E. Evaluation of patterns of liver toxicity in patients on antiretroviral and anti-tuberculosis drugs: a prospective four arm observational study in ethiopian patients. PloS one. 2014:9(4):e94271. doi: 10.1371/journal.pone.0094271.
78. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. American journal of respiratory and critical care medicine. 2002 Oct 1:166(7):916-9
79. Anand AC, Seth AK, Paul M, Puri P. Risk Factors of Hepatotoxicity During Anti-tuberculosis Treatment. Medical journal, Armed Forces India. 2006 Jan:62(1):45-9. doi: 10.1016/S0377-1237(06)80155-3.
80. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest. 1991 Feb:99(2):465-71
81. Zhao H, Wang Y, Zhang T, Wang Q, Xie W. Drug-Induced Liver Injury from Anti-Tuberculosis Treatment: A Retrospective Cohort Study. Medical science monitor : international medical journal of experimental and clinical research. 2020 Mar 7:26():e920350. doi: 10.12659/MSM.920350.
82. Aita JF, Calame TR. Peripheral neuropathy secondary to isoniazid-induced pyridoxine deficiency. Maryland state medical journal. 1972 Oct:21(10):68-70
83. Snider DE Jr. Pyridoxine supplementation during isoniazid therapy. Tubercle. 1980 Dec:61(4):191-6
84. Zilber La, Bajdakova Zl, Gardasjan An, Konovalov Nv, Bunina Tl, Barabadze Em. The Prevention And Treatment Of Isoniazid Toxicity In The Therapy Of Pulmonary Tuberculosis. 2. An Assessment Of The Prophylactic Effect Of Pyridoxine In Low Dosage. Bulletin of the World Health Organization. 1963:29(4):457-81
85. Martínez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin. Pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. Medicine. 1999 Nov:78(6):361-9
86. Girling DJ, Hitze KL. Adverse reactions to rifampicin. Bulletin of the World Health Organization. 1979:57(1):45-9
87. MacDougall C, Canonica T, Keh C, P Phan BA, Louie J. Systematic review of drug-drug interactions between rifamycins and anticoagulant and antiplatelet agents and

considerations for management. Pharmacotherapy. 2022 Apr:42(4):343-361. doi: 10.1002/phar.2672.
88. Kim HW, Kim JS. Treatment of Latent Tuberculosis Infection and Its Clinical Efficacy. Tuberculosis and respiratory diseases. 2018 Jan:81(1):6-12. doi: 10.4046/trd.2017.0052.
89. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1999 Oct:3(10):847-50
90. den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2016 Aug:20(8):1065-71. doi: 10.5588/ijtld.15.0908.
91. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerging infectious diseases. 2006 May:12(5):744-51
92. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, Menzies D, Horsburgh CR Jr, Crane CM, Burgos M, LoBue P, Winston CA, Belknap R. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports. 2020 Feb 14:69(1):1-11. doi: 10.15585/mmwr.rr6901a1.
93. Hirsch-Moverman Y, Colson PW, Bethel J, Franks J, El-Sadr WM. Can a peer-based intervention impact adherence to the treatment of latent tuberculous infection? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013 Sep:17(9):1178-85. doi: 10.5588/ijtld.12.0823.
94. Kahwati LC, Feltner C, Halpern M, Woodell CL, Boland E, Amick HR, Weber RP, Jonas DE. Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016 Sep 6:316(9):970-83. doi: 10.1001/jama.2016.10357.
95. US Preventive Services Task Force, Mangione CM, Barry MJ, Nicholson WK, Cabana M, Chelmow D, Coker TR, Davis EM, Donahue KE, Jaén CR, Li L, Ogedegbe G, Rao G, Ruiz JM, Stevermer J, Underwood SM, Wong JB. Screening for Latent Tuberculosis Infection in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2023 May 2:329(17):1487-1494. doi: 10.1001/jama.2023.4899.
96. Kunin M, Timlin M, Lemoh C, Sheffield DA, Russo A, Hazara S, McBride J. Improving screening and management of latent tuberculosis infection: development and evaluation of latent tuberculosis infection primary care model. BMC infectious diseases. 2022 Jan 12:22(1):49. doi: 10.1186/s12879-021-06925-8.
97. Kerani RP, Shapiro AE, Strick LB. A Pilot TB Screening Model in a U.S. Prison Population Using Tuberculin Skin Test and Interferon Gamma Release Assay Based on Country of Origin. Journal of correctional health care : the official journal of the National Commission on Correctional Health Care. 2021 Dec:27(4):259-264. doi: 10.1089/jchc.19.07.0056.
98. Rendleman NJ. Mandated tuberculosis screening in a community of homeless people. American journal of preventive medicine. 1999 Aug:17(2):108-13
99. Mehta B, Zapantis E, Petryna O, Efthimiou P. Screening Optimization of Latent Tuberculosis Infection in Rheumatoid Arthritis Patients. Arthritis. 2015:2015():569620. doi: 10.1155/2015/569620.