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DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION IN ADULTS

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Abstract

Latent tuberculosis infection (LTBI) remains a significant global public health concern. Approximately one-quarter of the world's population is estimated to be infected with Mycobacterium tuberculosis, with most individuals harboring the bacteria in a latent state. Although these individuals do not exhibit symptoms and are not contagious, they remain at risk of developing active tuberculosis (TB) disease during their lifetime. Early diagnosis of LTBI is essential for preventing disease progression and reducing TB transmission. This article reviews the epidemiology, risk factors, diagnostic methods, advantages and limitations of available tests, and current recommendations for diagnosing latent tuberculosis infection in adults.

Keywords: Latent tuberculosis infection, tuberculosis, diagnosis, tuberculin skin test, interferon-gamma release assay, adults.

Introduction

Tuberculosis (TB) remains one of the most significant infectious diseases worldwide. Despite advances in prevention and treatment, millions of people continue to be infected with Mycobacterium tuberculosis. According to

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international estimates, nearly 25% of the global population has latent tuberculosis infection (LTBI).

Latent tuberculosis infection is characterized by the presence of viable M. tuberculosis bacteria within the host without clinical manifestations of active disease. Individuals with LTBI do not experience symptoms and cannot transmit infection to others. However, they remain at risk of progressing to active tuberculosis, particularly when immune function is compromised.

The diagnosis of LTBI is an essential component of global tuberculosis elimination strategies. Effective screening allows healthcare professionals to identify high-risk individuals and initiate preventive treatment before active disease develops. Nevertheless, diagnosing LTBI remains challenging because there is no universally accepted gold standard test.

The aim of this study is to review current diagnostic approaches for latent tuberculosis infection in adults and evaluate their effectiveness, advantages, and limitations.

Methods

This study was conducted as a narrative literature review. Scientific publications, clinical guidelines, and international recommendations published by the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and other recognized healthcare organizations were analyzed.

The review focused on:

- Epidemiology of latent tuberculosis infection;
- Immunological basis of LTBI diagnosis;
- Tuberculin Skin Test (TST);
- Interferon-Gamma Release Assays (IGRAs);
- Clinical recommendations for adult screening.

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Relevant articles published in peer-reviewed journals were selected using databases such as PubMed, Scopus, and Google Scholar. Studies published in English within the last decade were prioritized.

Table 1. Estimated Prevalence of LTBI by Region

Region	Estimated LTBI Prevalence (%)
Africa	30–40
Southeast Asia	35–45
Western Pacific	25–35
Europe	10–20
Americas	5–15
Global Average	~25

The risk of latent infection is higher among:

- Healthcare workers;
- Close contacts of TB patients;
- Individuals with HIV infection;
- Patients receiving immunosuppressive therapy;
- Prison populations;
- Migrants from high TB burden countries.

Pathogenesis of Latent Tuberculosis Infection

After inhalation of infectious droplets containing Mycobacterium tuberculosis, bacteria reach the alveoli of the lungs. The immune system responds by activating macrophages and T-lymphocytes.

In most cases, the immune response successfully contains the bacteria within granulomas, preventing active disease development.

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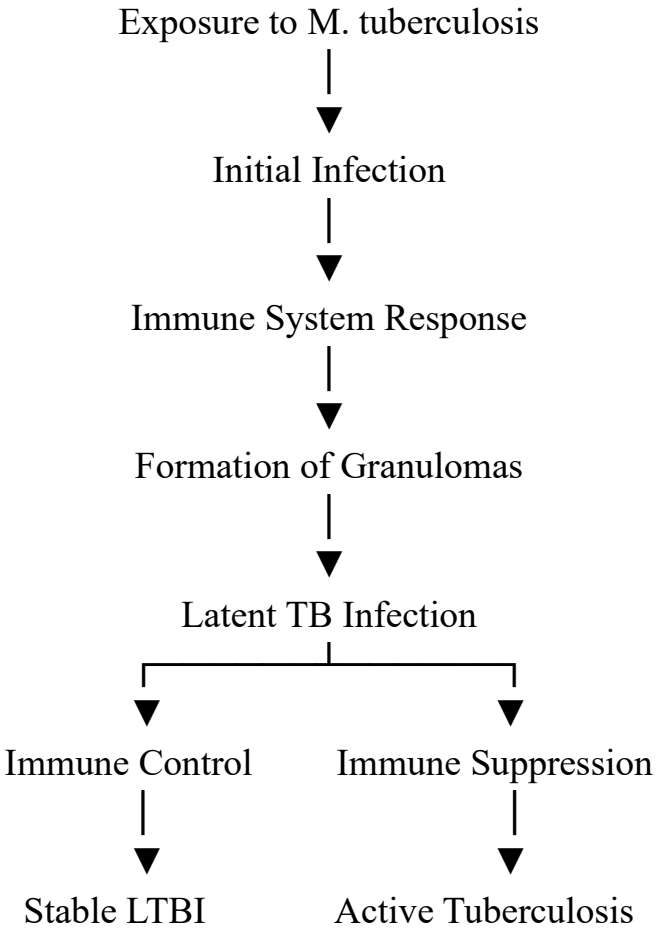
Figure 1. Development of Latent Tuberculosis Infection



Diagnostic Methods for LTBI

Currently, two main methods are recommended for diagnosing latent tuberculosis infection:

1. Tuberculin Skin Test (TST);
2. Interferon-Gamma Release Assays (IGRAs).

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Neither test can distinguish latent infection from active tuberculosis. Therefore, clinical evaluation and radiological assessment remain essential.

The Tuberculin Skin Test, also known as the Mantoux test, has been used for over a century.

The procedure involves intradermal injection of purified protein derivative (PPD) into the forearm. The size of induration is measured 48–72 hours later.

Figure 2. Tuberculin Skin Test Procedure

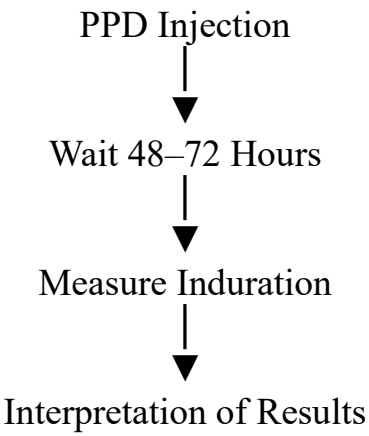

Table 2. Interpretation of TST Results

Induration Size	Interpretation
≥5 mm	Positive in high-risk individuals
≥10 mm	Positive in moderate-risk groups
≥15 mm	Positive in low-risk individuals

IGRAs are blood tests that measure immune responses to specific tuberculosis antigens.

The two most commonly used assays are:

- QuantiFERON-TB Gold Plus
- T-SPOT.TB

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These tests detect interferon-gamma production by T-cells following exposure to M. tuberculosis-specific antigens.

Figure 3. IGRA Testing Process

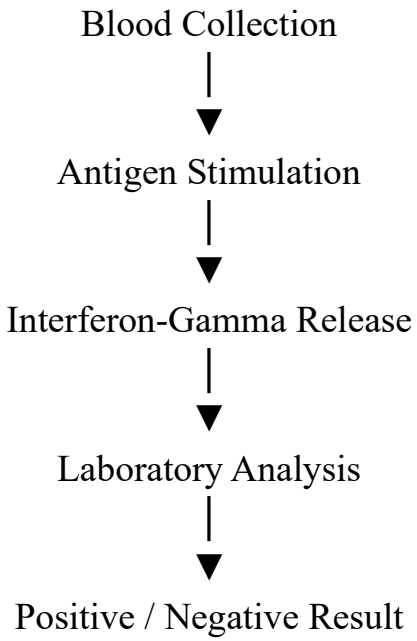

Table 3. Comparison of Diagnostic Methods

Characteristic	**TST**	**IGRA**
Cost	Low	High
Number of Visits	Two	One
BCG Interference	Yes	No
Specificity	Moderate	High
Sensitivity	Moderate	High
Laboratory Required	No	Yes

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Discussion

The diagnosis of latent tuberculosis infection remains one of the most important components of global tuberculosis prevention strategies. Although significant progress has been achieved in the development of diagnostic tools, identifying individuals with LTBI continues to present several clinical and public health challenges.

The findings of this review demonstrate that both the Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRAs) are effective methods for detecting an immune response to Mycobacterium tuberculosis. However, neither method is capable of directly detecting viable bacteria or accurately predicting which individuals will eventually develop active tuberculosis. Consequently, positive test results should always be interpreted within the context of clinical history, risk factors, and radiological findings.

The Tuberculin Skin Test remains the most widely used screening tool worldwide due to its simplicity, low cost, and minimal equipment requirements. In many low- and middle-income countries, TST continues to be the primary method for LTBI screening because healthcare resources are often limited. Despite these advantages, the test has several important limitations. Previous BCG vaccination may result in false-positive reactions, reducing test specificity. In addition, exposure to environmental non-tuberculous mycobacteria may influence test results. Another practical limitation is the requirement for a second patient visit within 48–72 hours for result interpretation, which may reduce compliance and increase the number of incomplete evaluations.

Interferon-Gamma Release Assays have emerged as valuable alternatives to TST. Their main advantage lies in the use of tuberculosis-specific antigens that are not present in BCG vaccines, leading to improved specificity. This characteristic is particularly important in countries where universal BCG vaccination is routinely administered. Furthermore, IGRAs require only a single patient visit and provide objective laboratory-based results, minimizing observer variability. Nevertheless,

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the higher cost of these assays and the need for specialized laboratory infrastructure may restrict their implementation in resource-limited healthcare systems.

An important consideration is the performance of diagnostic tests in immunocompromised populations. Individuals living with HIV infection, organ transplant recipients, patients receiving biologic therapies, and those undergoing chemotherapy are at increased risk of progressing from latent infection to active disease. However, immunosuppression may also reduce the sensitivity of both TST and IGRA tests, leading to false-negative results. This limitation highlights the importance of combining laboratory testing with comprehensive clinical assessment and risk stratification.

The results of recent studies suggest that neither TST nor IGRA should be viewed as standalone diagnostic tools. Instead, they should be integrated into broader screening programs that include epidemiological evaluation, chest radiography, and assessment of individual risk factors. Such an integrated approach improves diagnostic accuracy and helps identify patients who would benefit most from preventive treatment.

Another significant challenge is the absence of a true gold standard for latent tuberculosis infection diagnosis. Since LTBI represents a state of immune sensitization rather than active bacterial replication, direct microbiological confirmation is generally not possible. As a result, current diagnostic methods assess immune responses rather than the presence of viable organisms. This limitation contributes to uncertainty in estimating the true prevalence of LTBI and complicates comparisons between studies conducted in different populations.

Future developments in LTBI diagnostics are expected to focus on the identification of biomarkers capable of predicting progression to active tuberculosis. Advances in transcriptomics, proteomics, and immunological profiling have already identified several promising candidate biomarkers. Novel blood-based assays evaluating host gene expression signatures may improve risk

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prediction and allow clinicians to distinguish individuals at highest risk of disease progression. Artificial intelligence and machine learning technologies may further enhance diagnostic accuracy by integrating laboratory, radiological, and epidemiological data.

Conclusion

Latent tuberculosis infection continues to represent a major global health concern and serves as a substantial reservoir for future cases of active tuberculosis. Although individuals with LTBI are asymptomatic and non-infectious, the risk of progression to active disease remains significant, particularly among vulnerable populations with impaired immune function.

This review highlights the central role of the Tuberculin Skin Test and Interferon-Gamma Release Assays in the diagnosis of latent tuberculosis infection. Both methods provide valuable information regarding previous exposure to Mycobacterium tuberculosis and remain essential components of modern tuberculosis control programs. The Tuberculin Skin Test remains an important option in settings with limited resources because of its affordability and widespread availability. In contrast, IGRAs offer improved specificity and greater convenience, especially in BCG-vaccinated populations and in healthcare systems with adequate laboratory capacity.

Despite their widespread use, current diagnostic methods possess important limitations. Neither TST nor IGRA can reliably distinguish latent infection from active tuberculosis, quantify bacterial burden, or accurately predict future disease progression. Therefore, clinical judgment, radiological assessment, and evaluation of epidemiological risk factors remain indispensable components of the diagnostic process.

The growing burden of tuberculosis in many regions of the world underscores the importance of expanding LTBI screening programs, particularly among high-risk populations such as healthcare workers, household contacts of tuberculosis

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patients, individuals living with HIV, transplant recipients, and patients receiving immunosuppressive therapy. Early identification and treatment of latent infection can significantly reduce the likelihood of active disease development and contribute to tuberculosis elimination efforts.

In conclusion, effective diagnosis of latent tuberculosis infection remains a cornerstone of global tuberculosis prevention. Continued investment in research, diagnostic innovation, and targeted screening initiatives will be essential for reducing the burden of tuberculosis and achieving long-term public health goals worldwide.

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