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Review Article

Screening for latent TB: A review of interferon-gamma release assays and the tuberculin skin test (TST)

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Abstract

Latent tuberculosis infection (LTBI) affects a substantial portion of the global population and represents a key reservoir for future active tuberculosis (TB) cases. Early and accurate detection of LTBI is essential for TB control and elimination strategies, particularly in high-burden countries like India. The Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRAs), including QuantiFERON-TB Gold and T-SPOT.TB, are the principal diagnostic tools for LTBI. TST is simple, low-cost, and suitable for peripheral healthcare settings, but its specificity is limited by prior BCG vaccination and environmental non-tuberculous mycobacteria. IGRAs provide improved specificity by detecting T-cell responses to Mycobacterium tuberculosis-specific antigens, offer single-visit testing, and are particularly useful in immunocompromised or BCG-vaccinated populations. This review evaluates the diagnostic principles, comparative performance, predictive value for progression to active TB, operational challenges, cost-effectiveness, and guideline-based recommendations for TST and IGRA. Emphasis is placed on India-specific implementation strategies, including tiered diagnostic approaches, quality assurance, and use in special populations, highlighting the potential of these tools to optimize LTBI screening and accelerate progress toward national TB elimination goals.

Keywords: Latent TB infection, TST, Mantoux test, IGRA, QuantiFERON, T-SPOT.TB, Diagnostic accuracy, Predictive value, Guideline recommendations.

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1. Introduction

Tuberculosis (TB) continues to pose a significant public health challenge worldwide, with latent tuberculosis infection (LTBI) affecting an estimated 25% of the global population.[1] Although LTBI is asymptomatic and non-infectious, approximately 5–10% of infected individuals may progress to active TB, particularly those belonging to high-risk groups such as close contacts of TB patients, healthcare professionals, and immunocompromised individuals, including those living with HIV, diabetes mellitus, or undergoing immunosuppressive therapy.[2,3] Timely identification and management of LTBI remain critical components of the WHO End TB Strategy and other global TB elimination initiatives.

A growing concern in TB management is the emergence of multi-drug resistant (MDR) strains of TB, which are more difficult to treat and have higher rates of transmission. It is estimated that three of every 1,000 individuals worldwide have latent MDR tuberculosis infection, with incidence rates significantly higher among individuals younger than 15 years. If current trends persist, the proportion of latent TB caused by MDR strains will increase, posing significant challenges to TB control efforts.[20]

Historically, the Tuberculin Skin Test (TST), commonly referred to as the Mantoux test, has been the standard tool for LTBI detection. However, its diagnostic accuracy is limited by false-positive results, largely due to cross-reactivity with Bacille Calmette-Guérin (BCG) vaccination and exposure to environmental non-tuberculous mycobacteria (NTM)[^4]. In recent years, Interferon-Gamma Release Assays (IGRAs)—notably QuantiFERON-TB Gold and T-SPOT. TB—have emerged as valuable alternatives. These assays enhance specificity by detecting interferon-gamma (IFN-γ) released from sensitized T lymphocytes upon exposure to Mycobacterium tuberculosis-specific antigens such as

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ESAT-6 and CFP-10, which are absent in BCG strains and most NTMs.[3,5]

This article presents a narrative review of current evidence and guideline recommendations concerning the use of TST and IGRA for latent tuberculosis screening.

2. Discussion

2.1. Diagnostic principles

The Tuberculin Skin Test (TST), or Mantoux test, involves the intradermal administration of purified protein derivative (PPD) and subsequent measurement of induration after 48 to 72 hours. Though the test is cost-effective and simple to administer, its interpretation can be complicated by previous Bacillus Calmette-Guérin (BCG) vaccination and sensitization to environmental non-tuberculous mycobacteria (NTM), resulting in false-positive outcomes.[4,6]

In contrast, Interferon-Gamma Release Assays (IGRAs) are laboratory-based in vitro tests that evaluate interferon-gamma (IFN-γ) production by T lymphocytes in response to *Mycobacterium tuberculosis*-specific antigens such as ESAT-6 and CFP-10. These antigens are absent in BCG strains and most NTM, thereby enhancing the specificity of the assay and eliminating the need for return visits required by TST.[3,5,7]

2.2. Test performance

Comparative studies indicate that IGRAs have superior diagnostic performance compared to TST across several clinical settings. A robust meta-analysis found that TST sensitivity was significantly impaired in immunocompromised individuals, whereas IGRA performance remained relatively consistent.[1] In a large prospective cohort of 50,592 individuals, the relative risk (RR) of progression to active TB among IGRA-positive subjects was 9.35, compared to 4.24 for TST-positive individuals. The corresponding positive predictive values (PPV) were approximately 4.5% for IGRA and 2.3% for TST.[6]

Furthermore, data from low-TB-incidence countries confirmed the superior prognostic accuracy of IGRA.[7] Among healthcare workers, the T-SPOT.TB assay demonstrated a sensitivity of 92% and specificity of 95.7%, substantially outperforming the TST, which showed 76.5% sensitivity and 77.2% specificity.[8]

2.3. Special populations

Test performance varies significantly across population groups. A cohort study in South India found IGRA positivity in 57.6% of individuals compared to 49% with TST, with a low inter-test agreement of just 37%.[9] In a study among diabetic individuals in Yemen, both tests showed moderate concordance (kappa = 0.67), suggesting variable overlap in detection capacity.[10]

In HIV-infected individuals, IGRAs generally yield higher detection rates than TST, although indeterminate results are more common, particularly in patients with advanced immunosuppression and low CD4 counts.[2,7,13]

For pediatric populations, TST remains the primary screening tool due to limited validation of IGRA in younger age groups and lack of infrastructure. However, recent studies indicate that Operational and Economic Considerations.

The TST is favored in resource-limited settings due to its affordability, ease of use, and minimal infrastructural requirements. However, it necessitates a follow-up visit for result interpretation and may exhibit the "booster phenomenon" with repeated administration, complicating serial testing.[4,11]

IGRAs, while more costly and requiring specialized laboratory facilities and trained personnel, offer logistical advantages such as single-visit completion and are therefore better suited for populations where follow-up is challenging. These characteristics make IGRAs ideal for serial screening among healthcare workers or mobile populations, despite their limited accessibility in many low- and middle-income countries (LMICs).[3,11,16]

Beyond operational and financial considerations, the practical use of TST and IGRA is shaped by issues such as reproducibility, specimen transport, pre-analytical handling, and overall quality assurance. **Table 1** outlines these common pitfalls along with feasible programmatic solutions.

In the Indian context, embedding these strategies within the framework of the National TB Elimination Programme (NTEP) is essential. For instance, ensuring uninterrupted cold-chain maintenance for purified protein derivative (PPD) can improve the reliability of TST, while gradual incorporation of IGRA—particularly in well-equipped urban laboratories—may strengthen diagnostic accuracy and consistency in latent TB infection detection.[25,26] Current NTEP policy discussions emphasize the importance of integrating preventive therapy with modern diagnostic approaches.[27,28] Furthermore, recent evaluations demonstrate that, despite logistical barriers, IGRA deployment is feasible and can serve as a complementary tool in high-burden populations.[26,29] If implemented on a wider scale, these measures could accelerate progress toward India's 2025 TB elimination goal.[27,30]

Table 1: Common pitfalls and programmatic solutions for TST and IGRA[21-24]

Aspect	TST (Tuberculin Skin Test)	IGRA (QuantiFERON, T-SPOT.TB)	Suggested Programmatic Solutions
Reproducibility	Prone to inter-reader variation (2–3 mm differences common); must be read within 48–72 hours	Results fluctuate near cutoff; conversions/reversions occur in serial testing	Standardized training, blinded double-reading audits for TST; adoption of "borderline zones" and repeat testing strategies for IGRA
Patient logistics	Requires patient to return for reading; high rates of missed follow-up	One-time blood draw avoids repeat visits	Use digital/mobile reminders for TST follow-up; prioritize IGRA in populations with poor return compliance
Pre-analytical handling	PPD requires refrigeration (2–8 °C) and light protection	QFT tubes must be filled exactly (1 mL), shaken, and incubated within 16 h; T-SPOT requires PBMC processing within 8 h (extendable with T-Cell Xtend)	Strengthen supply chain cold-chain monitoring; provide standardized phlebotomy training; introduce stabilizing agents or extended incubation kits
Specimen transport	PPD stability maintained if cold chain is ensured in the field	QFT samples can be transported at room temperature but must reach lab within 16 h; T-SPOT requires stricter timelines	Establish regional processing hubs; optimize courier/logistics with temperature tracking; use point-of-care incubation devices
Error sources	Misplacement of intradermal injection, incorrect measurement of induration, booster phenomenon	Delayed incubation, tube under/overfilling, inadequate shaking, or temperature fluctuations	Develop competency-based training; use checklists and digital timers; introduce pre-filled devices and automated incubators
Operational challenges	High rates of no-shows for reading, especially in rural/remote settings	Needs well-equipped labs, ELISA/ELISPOT readers, and trained technicians	Deploy community health workers for TST reading; invest in central reference labs for IGRA with transport networks
Quality monitoring	Dependent on regular retraining and inter-reader reliability checks	Relies on monitoring indeterminate results, internal QC, and assay performance tracking	Implement external quality assurance schemes; set thresholds for indeterminate results; regular proficiency testing
Cost implications	Low direct cost but hidden costs due to repeat visits and misreadings	Higher upfront price, but savings from single-visit design and fewer repeats	Perform cost-effectiveness analysis tailored to region; consider hybrid models (TST for screening, IGRA for confirmation)

2.4. Operational challenges

Although IGRAs provide higher specificity than TST, their implementation in many low- and middle-income countries faces significant operational barriers, including dependence on specialized laboratories, trained personnel, and strict sample-handling requirements. To overcome these challenges, potential solutions include establishing centralized reference laboratories with reliable specimen transport systems, fostering public–private partnerships to expand diagnostic coverage, and adopting phased implementation strategies that prioritize high-burden or high-risk populations first. Such measures, when aligned with national tuberculosis elimination program frameworks, can improve access, ensure quality control, and enhance the cost-effectiveness of IGRA deployment.[31-33]

2.5. Cost-effectiveness considerations

Cost remains a critical determinant in scaling up TST and IGRA testing, particularly in low- and middle-income countries (LMICs). While TST is generally cheaper, it requires multiple patient visits and has logistical limitations, including maintaining cold chains and trained personnel. In contrast, IGRAs, though more expensive, offer higher specificity and require only a single visit, which may improve adherence and reduce hidden system costs.

Recent evaluations provide quantitative insights. A Brazilian study among healthcare workers demonstrated that novel TB antigen-based skin tests were cost-effective alternatives to QuantiFERON-TB Gold Plus (QFT-Plus), balancing affordability and diagnostic accuracy in resource-constrained settings.[34] Similarly, modeling studies in immigration screening found IGRA-based strategies more cost-effective in preventing future active TB cases in low-incidence countries compared to TST.[35] Another economic analysis highlighted that antigen-based skin tests may reduce overall programmatic costs in high-burden LMIC contexts, provided test pricing remains competitive.[36]

However, local implementation challenges persist. Indian and global perspectives underscore that hidden costs—such as patient follow-up, infrastructure, and staff training—often outweigh direct test costs.[32] Furthermore, updated procurement data from the Stop TB Partnership indicate significant price variations across countries, influencing national policy decisions.[33] Taken together, policymakers must balance upfront expenditure against long-term benefits in reducing TB incidence.

2.6. Predictive value for active TB

Both TST and IGRA demonstrate high negative predictive values (NPV), yet their positive predictive values (PPV) are modest. Nevertheless, IGRA-positive individuals have a higher likelihood of developing active TB. A prospective cohort study affirmed this increased risk, reinforcing the role of IGRA in identifying candidates for LTBI treatment in targeted prevention programs.[6,7,12]

2.7. Guideline-based recommendations

The 2024 WHO operational handbook (Module 3) supports the use of either TST or IGRA for LTBI detection. It advocates the use of IGRA in individuals who have received BCG vaccination or in settings where repeat visits for TST interpretation are impractical.[5,6,17]

The National Tuberculosis Elimination Programme (NTEP), India (2021), recommends both modalities, reserving TST for primary health centers and peripheral clinics, while suggesting IGRA use for immunocompromised patients and BCG-vaccinated populations when feasible.[18] Moreover, the Index TB guidelines endorse IGRA in children aged above five years and in occupational health screenings, reflecting evolving national diagnostic policies.[19]

2.8. India-specific diagnostic algorithms

The choice between TST and IGRA in India should reflect the level of healthcare facility and patient context, as outlined by the Central TB Division guidelines.[18]

1. Peripheral centers (PHCs, rural clinics): TST is preferred due to its low cost and ease of administration, provided cold-chain and trained staff are available.
2. Tertiary hospitals and urban laboratories: IGRA is more suitable where laboratory capacity exists, especially for immunocompromised patients, BCG-vaccinated individuals, or those requiring pre-transplant/biologic therapy screening.
3. Occupational health and healthcare workers: IGRA is favored for its higher specificity and single-visit format, reducing false positives and follow-up challenges.

A tiered approach—TST in peripheral facilities, with IGRA reserved for high-risk or specialized groups in advanced centers—aligns with the NTEP framework and can optimize resource use while improving diagnostic accuracy.

Table 2: Comparative Attributes of TST and IGRA in LTBI diagnosis

Attribute	Tuberculin Skin Test (TST)	Interferon-Gamma Release Assays (IGRAs)
Cost	Low (inexpensive)	High (test kits, lab infrastructure)
Infrastructure	Minimal (PPD, trained staff)	Requires specialized laboratory & equipment
Turnaround Time	48–72 hours (requires 2 visits)	24 hours (single visit, but processing time dependent)
Sensitivity	Moderate; affected by immunosuppression	Moderate–high; variable in immunocompromised
Specificity	Lower (cross-reactivity with BCG and NTM)	Higher (does not cross-react with BCG)
Ease of Use	Simple, field-friendly	Requires phlebotomy, lab handling
Suitability – HIV	Reduced accuracy (anergy possible)	Indeterminate results common; needs careful interpretation
Suitability – Pediatrics	Limited reliability in <5 years	Blood volume issues; limited pediatric data
Use in Mass Screening	Feasible, low-cost	Limited due to cost/logistics

2.9. Special population nuances

Certain populations present unique challenges in the interpretation of latent TB diagnostics (**Table 2**)

1. Immunocompromised individuals, especially those with HIV and low CD4+ counts, have significantly higher rates of indeterminate IGRA results; for instance, one meta-analysis noted that 1 in 26 IGRA tests overall yielded indeterminate findings, and the odds were elevated in HIV-positive patients.[37,38]
2. In pediatric populations, especially children under five years, both TST and IGRA face limitations—IGRA performance is less predictable due to immature immune responses, variable indeterminate rates (0–17%), and the practical difficulty of drawing sufficient blood volume; meta-analyses report around 4% indeterminate IGRA results in children, with immunocompromise further increasing this risk.[39-41]

3. Conclusion

This review provides a comprehensive comparison of TST and IGRA for latent tuberculosis screening, highlighting their respective strengths and limitations in the Indian context. Incorporating discussions on operational challenges, cost-effectiveness, and context-specific diagnostic algorithms can further strengthen its practical relevance. By addressing these aspects, the article can serve as a valuable resource to guide evidence-based decision-making and optimize screening strategies within India's TB control framework. Looking ahead, embedding these approaches into the National TB Elimination Programme through phased implementation, quality assurance, and targeted use in high-risk groups, along with continued investment in novel diagnostics such as biomarker-based assays and next-generation immunological tests, will be essential to accelerate India's progress toward TB elimination.

4. Source of Funding

None.

5. Conflict of Interest

None.

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