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From Mantoux to Cy-Tb: Diagnostic Advances, Clinical Applications and Future Directions in Tuberculosis Infection Screening

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Abstract

Tuberculosis (TB) infection constitutes a vast reservoir from which future TB disease arises, making reliable identification of infected individuals central to preventive treatment and global elimination strategies. For more than a century, the Mantoux tuberculin skin test (TST) has been the principal field-based immunological test for TB infection. Its affordability and operational simplicity have sustained its use, but purified protein derivative contains antigens shared with bacille Calmette-Guérin (BCG) strains and several nontuberculous mycobacteria, reducing specificity in many populations. Interferon-gamma release assays (IGRAs) improved antigenic specificity by using early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10), but their cost, laboratory requirements, pre-analytical vulnerability and need for timely specimen processing restrict decentralised implementation. Cy-Tb is a newer Mycobacterium tuberculosis antigen-based skin test that delivers recombinant ESAT-6 and CFP-10 intradermally, seeking to combine the field practicality of the Mantoux test with specificity approaching that of IGRAs. This narrative review traces the evolution from TST to Cy-Tb, examines biological principles, administration, interpretation, diagnostic performance, safety, clinical and programmatic applications, and compares Cy-Tb with TST and IGRAs. WHO recommendations, Indian National Tuberculosis Elimination Programme relevance, recent multicentre Indian evidence and implementation challenges are discussed. Cy-Tb is a promising tool for expanding targeted testing among household contacts, people living with HIV, healthcare workers and other at risk populations, particularly in high burden, BCG vaccinated settings. However, it remains an indirect test of host immune sensitisation: it cannot independently distinguish cleared infection, persistent infection and active TB disease, cannot determine drug susceptibility, and requires a return visit for reading. Its public health effect will therefore depend on correct placement within a complete cascade that excludes active disease, links eligible individuals to tuberculosis preventive treatment, assures quality, and measures outcomes. Future priorities include prospective predictive value studies, evidence in young children and immunocompromised populations, operational cost effectiveness analyses, digital reading systems and surveillance of real world performance.

Keywords: Cy-Tb; tuberculosis infection; Mantoux test; tuberculin skin test; ESAT-6; CFP-10; interferon gamma release assay; tuberculosis preventive treatment; latent tuberculosis infection; TB antigen based skin test

1. Introduction

Tuberculosis remains one of the world's most consequential infectious diseases. The burden is sustained not only by people with untreated infectious pulmonary disease but also by the much larger pool of individuals with immunological evidence of infection who may develop disease later. The term "latent tuberculosis infection" has traditionally described a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifest disease. Contemporary usage increasingly favours "tuberculosis infection" (TBI), acknowledging that infection exists along a biological spectrum rather than as a uniform dormant state. Neither terminology implies that viable bacilli can be directly demonstrated by existing routine immunological tests.

Testing for TBI is valuable only when the result will guide a clinical or public-health action. It is most commonly used to identify people who may benefit from tuberculosis preventive treatment (TPT), to support contact investigation and occupational-health programmes, and to evaluate selected immunocompromised patients before therapies that increase the risk of progression. Before TPT, active TB disease must be excluded by symptom assessment and, where indicated, chest imaging, microbiological or molecular testing and clinical evaluation. A positive immune-based test is not a diagnosis of active disease; conversely, a negative result cannot reliably exclude active disease, especially in young children and immunocompromised or severely ill patients.

The Mantoux TST became the archetypal field test because it is inexpensive, requires no laboratory and can be administered at peripheral facilities. Nevertheless, its antigenic complexity creates cross-reactivity after BCG vaccination and exposure to nontuberculous mycobacteria. IGRAs represented a major conceptual advance by using antigens more specific to the M. tuberculosis complex, but their infrastructure and cost requirements limit population-level deployment in many high-burden countries. M. tuberculosis antigen-based skin tests (TBSTs) were developed to bridge this gap. Cy-Tb, formerly called C-Tb, is one such test and uses recombinant ESAT-6 and CFP-10 antigens. WHO first recommended the class of TBSTs in 2022 as an option for testing for TBI.

This review examines how Cy-Tb changes the diagnostic landscape, with emphasis on clinical interpretation, comparative advantages, programmatic use in India and other high-burden settings, and the evidence still needed before its potential can be fully realised.

2. Review methodology

This narrative review was developed through a focused search of PubMed/MEDLINE, WHO publications and the WHO TB Knowledge Sharing Platform, the Indian National Tuberculosis Elimination Programme (NTEP) Knowledge Base, and reference lists of relevant trials and reviews. Searches covered literature available up to 29 August 2026 and used combinations of "Cy-Tb," "C-Tb," "tuberculosis antigen based skin test," "TBST," "ESAT-6," "CFP-10," "tuberculin skin test," "Mantoux," "interferon gamma release assay," "tuberculosis infection," "latent tuberculosis," "diagnostic accuracy," "safety," "cost effectiveness," "children," "HIV" and "India." Priority was given to WHO guidance, national programme documents, prospective clinical trials, multicentre diagnostic accuracy studies, systematic reviews and meta-analyses. Publications addressing administration, diagnostic performance, safety, operational feasibility, economics and special populations were included. Because no microbiological gold standard exists for TBI, accuracy estimates were interpreted in relation to the reference standards and populations used by each study. This was a narrative rather than a protocol

registered systematic review; therefore, pooled estimates were not recalculated and risk of bias was not independently graded.

3. Evolution of immunological testing for tuberculosis infection

3.1 The Mantoux tuberculin skin test

The Mantoux test measures delayed type hypersensitivity after intradermal injection of purified protein derivative (PPD). In a previously sensitised person, antigen presenting cells activate memory T lymphocytes, producing a local inflammatory response. Induration not erythema is measured transversely to the long axis of the forearm, usually 48-72 hours after administration. Interpretation depends on the product, national guidance, epidemiological context, risk group and chosen threshold.

TST has enduring strengths. It needs no phlebotomy or laboratory platform, has a low unit cost, and can be deployed in primary-care and outreach settings. Decades of use provide familiarity and evidence linking test positivity to subsequent risk of disease and benefit from preventive therapy. Yet PPD is a mixture of antigens, many shared by BCG vaccine strains and environmental mycobacteria. Consequently, false positive results may occur, particularly when BCG is given after infancy or repeatedly. False negative results can occur early after infection, in very young or older individuals, severe or disseminated TB, HIV infection, malnutrition, recent viral illness, immunosuppressive therapy and technical failure. Administration and reading are operator dependent; digit preference and inter reader variability can distort measurement. The need for a second visit causes attrition, while boosting on repeat testing complicates serial occupational screening.

3.2 Interferon-gamma release assays

IGRAs measure ex vivo interferon gamma release by sensitised T cells after stimulation with M. tuberculosis-specific antigens, principally ESAT-6 and CFP-10. These antigens are encoded within the region of difference 1, which is absent from BCG strains and most nontuberculous mycobacteria. This gives IGRAs greater specificity than TST in BCG vaccinated populations. A single patient visit is usually sufficient, and there is no boosting from repeated skin testing.

However, IGRAs exchange field simplicity for laboratory dependence. They require venepuncture, controlled transport, timely incubation or processing, trained laboratory staff, quality assurance and relatively expensive consumables and equipment. Indeterminate results occur, particularly with immunosuppression, young age, technical problems or inadequate mitogen response. Within person variability around the assay cut off can produce conversions and reversions in serial testing. Like TST, IGRAs measure immune memory rather than viable bacilli and cannot separate active from non-active infection or predict progression with high individual-level precision.

3.3 Emergence of antigen based skin tests

TBSTs transpose the antigenic specificity of IGRA onto the familiar intradermal skin test platform. WHO evaluated Cy-Tb, Diaskintest and C-TST and recommended TBSTs as an additional option for diagnosing TBI. The strategic proposition is attractive: a test that does not require blood collection or a laboratory, is minimally influenced by BCG vaccination, and can be implemented through existing skin-test workflows. The innovation lies not in measuring a new immune phenomenon, but in replacing the nonspecific antigen mixture of PPD with defined M. tuberculosis-specific antigens.

4. Cy-Tb: composition and immunological basis

Cy-Tb is an intradermal test containing recombinant ESAT-6 and CFP-10. These secreted proteins are

strongly recognised during natural M. tuberculosis infection but are absent from BCG vaccine strains. Following intradermal injection in a sensitised individual, antigen-specific memory T cells migrate to the site and generate a delayed hypersensitivity response, producing measurable induration.

The designation "specific" should be used carefully. ESAT-6 and CFP-10 are not exclusive to M. tuberculosis in an absolute taxonomic sense; a limited number of nontuberculous mycobacterial species may carry homologous antigens. Nevertheless, the practical cross-reactivity is substantially less than with PPD. Cy-Tb therefore improves specificity in BCG-vaccinated populations without eliminating every possible biological or technical false result.

Cy-Tb does not measure bacterial load, bacillary viability, anatomical disease, transmissibility or drug resistance. A positive result indicates a cell mediated immune response compatible with previous sensitisation to relevant antigens. It cannot tell when infection occurred or whether organisms have been cleared. Clinical decisions must integrate exposure history, age, immune status, time since contact, symptoms, imaging and disease investigations.

5. Administration, reading and interpretation

Cy-Tb is administered intradermally on the volar surface of the forearm by trained personnel using the manufacturer and programme-specified dose and technique. Correct placement should raise a small, pale wheal. A failed intradermal injection, leakage, subcutaneous delivery or incorrect dose can invalidate the response and should be managed according to the approved product information and programme protocol.

The reaction is read after the specified interval, generally using the same operational principles as TST. The transverse diameter of palpable induration is measured in millimetres with a transparent ruler; erythema is not used. WHO operational guidance and local product instructions should determine the exact reading window and threshold. Indian programme materials use a 5-mm induration threshold for Cy-Tb positivity. Programme staff should avoid importing risk-stratified Mantoux thresholds into Cy-Tb interpretation unless national guidance explicitly requires this.

Quality assurance is essential. Training should cover intradermal technique, recognition of a valid wheal, palpation, ballpoint pen or equivalent edge detection where recommended, transverse measurement, recording the exact millimetre value rather than only "positive" or "negative," infection prevention, adverse event advice and referral pathways. Periodic inter-reader assessments and supervision help prevent systematic over reading or under reading.

Test timing also matters. After a recent exposure, adaptive immune conversion may take several weeks. An initial negative test performed too early may need repetition after the window period specified by national guidance. A negative Cy-Tb result should be interpreted cautiously in infants, people living with advanced HIV, those receiving immunosuppressive therapies, patients with severe illness or malnutrition, and individuals with suspected active TB. In high risk young child contacts and some people living with HIV, eligibility for TPT may be determined programmatically after exclusion of active disease without requiring a positive infection test; current national guidance should prevail.

6. Diagnostic performance

6.1 The challenge of evaluating tests without a gold standard

There is no direct gold-standard test for asymptomatic TBI. Culture and nucleic-acid amplification detect TB disease, not the full spectrum of infection. Studies therefore use imperfect approaches:

microbiologically confirmed active TB as a proxy for sensitivity, low risk unexposed populations as a proxy for specificity, concordance with IGRA, or increasing positivity with epidemiological exposure. Each design answers a different question. Sensitivity calculated in active TB may be affected by disease-related immune suppression and may not equal sensitivity in healthy contacts. Agreement with IGRA is not proof of truth because both tests use overlapping antigens and reflect related immune pathways.

6.2 Trial evidence

Early phase studies established the dose and safety of recombinant ESAT-6/CFP-10 preparations. Subsequent C-Tb/Cy-Tb trials found positivity patterns broadly comparable to IGRA and greater specificity than PPD in BCG-vaccinated, low-risk participants. A phase 3 randomised controlled trial reported that C-Tb maintained high specificity irrespective of BCG status and had a safety profile compatible with clinical use. Studies among culture-confirmed TB cases suggested sensitivity similar to QuantiFERON-TB Gold In-Tube, although sensitivity was lower in HIV-infected participants, consistent with impaired cell-mediated immunity.

A systematic review and meta-analysis of novel skin-based tests found that C-Tb and other TBSTs generally had high specificity and diagnostic performance comparable to established tests, while also highlighting heterogeneity in populations, thresholds and reference standards. A 2024 diagnostic meta-analysis comparing IGRA, TST and TBST reinforced that performance varies by study design and immune status; no immune based test provides a definitive diagnosis of viable infection.

6.3 Recent Indian multicentre evidence

The 2026 Indian multicentre study by Singh and colleagues provides especially relevant programmatic evidence. In one component, Cy-Tb showed high agreement with IGRA, with reported specificity estimates of 90.0% and 93.8% in the evaluated groups, overall agreement of 91.9% and a Cohen kappa of 0.83. In combined subsequent components, using IGRA as the reference, Cy-Tb showed sensitivity of 82.6% (95% confidence interval [CI], 79.1-85.8), specificity of 71.1% (95% CI, 68.2-73.8), agreement of 74.8% and kappa of 0.5. In the same analysis, PPD showed sensitivity of 71.0% and specificity of 71.9%. The authors concluded that Cy-Tb performance was comparable to PPD, with IGRA as reference, and supported its use for detecting TBI.

These results require nuanced interpretation. The lower specificity in combined analyses compared with low-risk trial populations may reflect use of IGRA as an imperfect comparator, differences in exposure and participant spectrum, biological discordance, threshold effects or field conditions. A Cy-Tb-positive/IGRA-negative result is not automatically a Cy-Tb false positive. Conversely, shared ESAT-6/CFP-10 antigens can create correlated errors and inflate agreement. Real-world evaluation should therefore include exposure gradients, clinical outcomes and progression to disease, rather than agreement alone.

7. Comparative assessment of available tests

Characteristic	Mantoux TST	Cy-Tb	IGRA
Biological platform	In-vivo delayed hypersensitivity	In-vivo delayed hypersensitivity	Ex-vivo T-cell interferon-gamma response
Principal antigens	PPD mixture	Recombinant ESAT-6 and CFP-10	ESAT-6 and CFP-10-based peptides; assay-specific additions

Effect of BCG vaccination	May reduce specificity	Minimal expected effect	Minimal expected effect
Laboratory needed	No	No	Yes
Blood sample	No	No	Yes
Patient visits	Two in usual workflow	Two in usual workflow	Usually one
Result	Millimetres of induration	Millimetres of induration	Positive, negative or indeterminate with quantitative values
Operator dependence	Administration and reading	Administration and reading	Phlebotomy, transport, processing and laboratory interpretation
Indeterminate category	No formal category; anergy may appear negative	No formal category; anergy may appear negative	Yes
BCG/NTM cross-reactivity	Higher	Lower, but not theoretically zero	Lower, but not theoretically zero
Infrastructure suitability	Strong for peripheral settings	Strong for peripheral settings if supply and training are established	Better for laboratory-supported settings
Ability to diagnose active TB independently	No	No	No
Ability to determine drug resistance	No	No	No

Cy-Tb is best viewed as an additional option rather than a universal replacement for both TST and IGRA. A programme with robust IGRA laboratories and reliable specimen logistics may value the single-visit pathway. In decentralised or outreach settings, Cy-Tb can reduce laboratory dependence but retains the second-visit problem. TST may remain appropriate where cost is decisive and BCG related specificity is less problematic, or where procurement of newer tests is uncertain. Choice should reflect target population, BCG policy, prevalence, laboratory access, return rates, staff competencies, costs across the full cascade and the consequences of false positive and false negative decisions.

8. Clinical applications

8.1 Household and close contacts

Contact investigation is a central use case. Household contacts have a higher probability of infection and progression, particularly soon after exposure. Cy-Tb can provide a more specific field test in BCG-vaccinated populations, potentially reducing unnecessary preventive treatment among older contacts when testing is required. However, contacts must first be assessed for TB disease. Young children require special urgency because disease progression can be rapid and severe. Testing must never delay preventive treatment when national guidance recommends treatment on the basis of age and exposure after disease exclusion.

8.2 Children and adolescents

Intradermal testing avoids venepuncture and may be attractive in paediatric services. Specific antigens reduce confusion from routine neonatal BCG vaccination, a major advantage in India and many high-burden countries. Yet paediatric immune responses vary with age, nutrition and disease severity. Evidence remains less extensive in infants and very young children than in adults. A negative result cannot exclude infection or disease in a symptomatic child, a severely malnourished child, or a young recent contact. Paediatric interpretation should be exposure-led and embedded in a complete clinical algorithm.

8.3 People living with HIV and other immunocompromised populations

The risk of progression is high among people living with HIV, transplant candidates and recipients, patients receiving tumour necrosis factor inhibitors or other biological agents, and individuals receiving prolonged immunosuppression. Testing may support preventive decisions, but all T-cell dependent tests lose sensitivity as immune function deteriorates. Cy-Tb is not exempt from anergy. A negative test in a high-risk immunocompromised person may therefore have limited rule-out value. Some guidelines recommend TPT for people living with HIV after excluding active disease regardless of infection-test status. Testing strategies must not erect barriers to indicated prevention.

8.4 Healthcare workers and congregate settings

Healthcare workers, prison populations, miners, migrants, people in shelters and residents of other congregate environments may experience ongoing exposure. Cy-Tb could facilitate decentralised baseline or targeted testing. Serial-testing algorithms, however, require careful validation because biological and measurement variability can create apparent conversions or reversions near the threshold. Programmes should define conversion criteria, manage recent exposure appropriately and avoid indiscriminate mass testing where a positive result will not lead to intervention.

8.5 Pre-immunosuppression evaluation

Before anti-TNF therapy, transplantation or other potent immunosuppression, detecting TBI can prevent reactivation. In BCG-vaccinated patients without reliable IGRA access, Cy-Tb offers a specific alternative. When consequences of missing infection are substantial, clinicians may consider dual or sequential testing under applicable specialty and national guidance, particularly when clinical risk is high and the initial test is negative. Such approaches increase sensitivity but may reduce specificity and cost-effectiveness.

9. Programmatic relevance to India and other high-burden settings

India combines high TB transmission, near-universal BCG vaccination, large numbers of household contacts, marked diversity in laboratory access and an ambitious elimination programme. These conditions make a BCG independent, laboratory-free skin test operationally appealing. Cy-Tb can potentially be integrated into contact investigation, TPT services, HIV care, occupational health and selected community campaigns through existing NTEP structures.

Implementation must be designed around the complete preventive care cascade. The number tested is an inadequate success metric. Programmes should monitor eligibility assessment, valid test placement, return and reading, disease exclusion, TPT initiation, adverse event management, completion and subsequent TB disease. A test can have excellent analytical characteristics yet little population impact if people do not return or if positive individuals are not linked to care.

Supply-chain planning should include forecasting, cold chain and storage requirements in accordance with product instructions, lot tracking, expiry management, syringes and rulers, pharmacovigilance and waste disposal. Training should include counselling so patients understand that a positive test does not mean infectious disease and a negative result is not a guarantee of lifelong protection. Digital recording within routine surveillance systems may improve traceability and reduce loss between testing and treatment.

Introducing Cy-Tb also requires stewardship of existing resources. Parallel maintenance of PPD, Cy-Tb and IGRA pathways without clear indications may create duplication and inconsistent interpretation. National and local algorithms should specify the preferred test by population and setting, acceptable alternatives, management of discordance, retesting rules and referral criteria. Procurement price alone should not determine policy; total costs include staff time, return visits, laboratory transport avoided, false-positive preventive treatment, missed infection and patient expenses.

10. Safety and acceptability

Clinical trials and systematic safety reviews indicate that antigen-based skin tests are generally well tolerated. Expected reactions are mainly local-pain, itching, erythema, induration or swelling-and are usually mild and self-limited. Severe systemic hypersensitivity appears uncommon, but services must follow approved contraindications and be prepared to recognise and manage acute allergic reactions. Previous severe reaction to the product or its components requires particular caution according to the product label.

Acceptability depends on more than adverse events. Some patients prefer a skin test to blood collection; others find a second visit inconvenient. Large local reactions can cause anxiety and should be anticipated during counselling. Clear instructions should advise against scratching or applying unapproved creams and should explain when to seek care. Patient-reported experience, travel costs and return rates should be included in implementation evaluations.

11. Limitations and diagnostic pitfalls

The central limitation of Cy-Tb is shared by all current tests for TBI: it is an indirect measurement of host immunity, not a demonstration of living bacilli. Thus, positive predictive value for progression to TB disease is expected to be modest, especially in low-risk populations. Testing people with low pre-test probability can generate more harm than benefit through anxiety, further investigations and unnecessary treatment.

False-negative or attenuated responses may occur with recent infection, extremes of age, advanced HIV, severe TB disease, malnutrition, viral illness and immunosuppressive treatment. Technical errors in injection, timing or reading add avoidable misclassification. False-positive responses may arise through rare cross-reactive mycobacteria, measurement error or immune sensitisation that no longer represents viable infection. Prior TPT or successfully treated TB does not guarantee test reversion; Cy-Tb should not be used to monitor treatment response.

Cy-Tb cannot identify the site of disease, infectiousness or drug resistance. Any person with symptoms, abnormal imaging or clinical concern requires a diagnostic evaluation using bacteriological, molecular, radiological and clinical methods. In contacts of drug-resistant TB, the infection test cannot reveal whether the infecting strain is resistant; preventive-treatment choice must incorporate the source patient's drug-susceptibility pattern and current guidance.

The second-visit requirement is a major operational weakness. If reading is missed, the entire first encounter may yield no actionable result. Community reading, reminder systems, transport support, flexible clinic hours and validated digital tools may reduce attrition. Self-reading based only on photographs is not a substitute for validated measurement because palpation is required to distinguish induration from erythema.

12. Economic and health-system considerations

The economic question is not whether Cy-Tb costs more or less per vial than PPD or per assay than IGRA. The relevant comparison is cost per person completing an appropriate preventive-care pathway and, ultimately, cost per TB case averted. Cy-Tb may avoid laboratory equipment, phlebotomy, sample transport and indeterminate laboratory results. Higher specificity than PPD may reduce unnecessary TPT and associated monitoring. Conversely, two patient visits, staff time, wastage and loss to follow-up can erode these gains.

Economic models of TBSTs suggest that cost-effectiveness is highly dependent on local test prices, return rates, TB prevalence, TPT uptake and completion, and healthcare costs. Country-specific analyses should use real procurement and delivery data rather than extrapolating from trial conditions. Equity must also be considered: a decentralised test may improve access in remote settings, but only if reliable supply, trained readers and referral services reach those communities.

13. Future directions

The most important research need is prospective evidence linking Cy-Tb results to incident TB disease. Concordance with IGRA is useful, but the clinically meaningful outcome is progression and its prevention. Large longitudinal cohorts should estimate absolute risk across induration sizes, age groups, time since exposure, HIV status, nutritional status and comorbidities. Such data could support risk-stratified interpretation rather than a purely binary threshold.

More evidence is needed in infants, young children, pregnancy, advanced HIV, transplant populations, patients receiving new immunomodulators and contacts of drug-resistant TB. Studies should report invalid placements, missed readings, reader variability, adverse events and cascade outcomes, not only sensitivity and specificity. Head to head trials should use consistent thresholds and account for incorporation bias when IGRA is the comparator.

Digital innovation may improve administration and reading quality. Smartphone-assisted measurement, computer vision and electronic decision support could standardise documentation, flag implausible values and link results to surveillance systems. However, visible erythema cannot substitute for palpable induration, and algorithms require prospective validation across skin tones, devices and field conditions. Digital systems should support, rather than prematurely replace, trained clinical assessment.

Operational research should compare facility based, community based and household delivery models, including reminder strategies and task-sharing. Cluster randomised or pragmatic studies could determine whether Cy-Tb increases TPT initiation and completion and reduces incident disease compared with existing pathways. Cost effectiveness and budget-impact analyses should incorporate patient-incurred costs and equity. Post marketing surveillance should monitor rare adverse events, lot performance and changes in test positivity across epidemiological settings.

Finally, future diagnostics must move beyond the binary detection of immune memory. Biomarkers capable of identifying viable infection, incipient disease or near term progression would allow

preventive therapy to be concentrated among those most likely to benefit. Until such tests are validated and scalable, Cy-Tb offers an incremental but potentially important improvement: greater antigenic specificity on a platform suitable for decentralised care.

14. Practical clinical algorithm

1. Identify an individual for whom testing is recommended and for whom the result will influence management.
2. Assess TB exposure, symptoms, risk factors, previous TB/TPT and immune status.
3. Exclude active TB disease using the appropriate clinical, radiological and microbiological pathway; do not use Cy-Tb as a stand-alone rule-out test.
4. Select Cy-Tb, TST or IGRA according to national guidance, age, BCG status, laboratory access, likelihood of return and clinical risk.
5. Administer Cy-Tb intradermally using approved technique and record product and placement details.
6. Read at the specified interval, measure transverse induration in millimetres and interpret using the approved threshold.
7. For a positive result, re confirm that active disease has been excluded, counsel the patient and initiate an appropriate TPT regimen when eligible.
8. For a negative result, consider window-period repeat testing, immune suppression and age; do not allow a negative result to override strong clinical suspicion or programme-based TPT eligibility.
9. Record linkage to treatment, completion, adverse events and follow up outcomes.

15. Conclusion

The transition from Mantoux to Cy-Tb represents a rational evolution in TBI screening. By replacing the heterogeneous PPD antigen mixture with recombinant ESAT-6 and CFP-10, Cy-Tb seeks to preserve the accessibility of an intradermal test while reducing BCG-related false positivity and laboratory dependence. WHO endorsement of the TBST class and emerging Indian multicentre evidence support its inclusion among available testing options.

Cy-Tb is not, however, a stand-alone diagnostic solution. It cannot distinguish active disease from infection, prove bacillary viability, predict progression with high precision or determine drug susceptibility. Its accuracy is shaped by host immunity, timing and field technique, and its two visit workflow can lead to loss to follow up. The appropriate question is therefore not whether Cy-Tb should replace every Mantoux test or IGRA, but where it produces the greatest clinical and programmatic value. In high burden, BCG vaccinated settings, its strongest role may be targeted decentralised testing linked to reliable disease exclusion and TPT. If programmes invest equally in training, quality assurance, return-visit support, counselling, supply chains and outcome monitoring, Cy-Tb could help close the gap between identifying risk and preventing disease. Future longitudinal and implementation research should determine whether this diagnostic advance translates into fewer TB cases and more equitable preventive care.

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