



The Relationship between Mantoux Sensitivity and The Diagnosis of Childhood Tuberculosis : A Comprehensive Systematic Review

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ABSTRACT

Introduction: Childhood tuberculosis (TB) remains a significant global health challenge, with diagnostic difficulties compounded by nonspecific clinical presentations and limitations of available tests. The Mantoux tuberculin skin test (TST) has been a cornerstone of TB diagnosis for decades, yet its accuracy in children remains controversial due to factors including BCG vaccination, age-related immune responses, and comorbidities. This systematic review aims to comprehensively evaluate the relationship between Mantoux test sensitivity and the diagnosis of childhood tuberculosis.

Methods: A systematic review was conducted following PRISMA guidelines. We screened studies based on predefined criteria

including pediatric population (0-18 years), TST evaluation against reference standards, and reporting of diagnostic performance data. Seventy-five studies comprising systematic reviews, meta-analyses, diagnostic accuracy studies, cohort studies, and cross-sectional investigations were included. Data extraction encompassed study characteristics, TST protocols, reference standards, diagnostic performance metrics, comparison with IGRAs, population risk factors, and clinical context.

Results: Pooled TST sensitivity for active TB in children ranged from 64% to 86% across major meta-analyses, with the highest values (82-86%) observed in microbiologically confirmed cases in high-income countries and lower values (64-74%) in low-income settings or clinically diagnosed cases. Specificity ranged from 49% in BCG-vaccinated populations to 92% in high-income settings without BCG. For latent TB infection, TST sensitivity was estimated at 82% with specificity of 98% in non-BCG and 82% in BCG-vaccinated children. Head-to-head comparisons showed IGRAs demonstrate superior specificity (85-98% vs. 56-92%), particularly in BCG-vaccinated populations, while sensitivity comparisons varied by context. Age <5 years, HIV infection, malnutrition, and helminth co-infection significantly reduced TST sensitivity. Novel antigen-specific skin tests (C-Tb, ECST, Diaskintest) showed IGRA-like specificity (94-97%) unaffected by BCG.

Discussion: TST performance in children is highly context-dependent, with BCG vaccination status, age, geographic setting, and comorbidities serving as critical determinants. The apparent paradox of variable TST-IGRA comparisons is explained by population differences: TST may be more sensitive in high-burden

settings where case detection is paramount, while IGRAs offer superior specificity in low-incidence, BCG-vaccinated populations. The diagnostic gap in children under 5 years—where both tests perform poorly—represents a critical challenge. Sequential testing strategies and novel skin tests offer promising alternatives.

Conclusion: The Mantoux test remains a valuable tool for childhood TB diagnosis, but its limitations must be understood contextually. No single test is universally superior; test selection should be guided by local epidemiology, BCG vaccination policies, and available resources. Future research should focus on validating novel skin tests in pediatric populations and developing integrated diagnostic algorithms for young and immunocompromised children.

Keywords: Childhood tuberculosis, Mantoux test, tuberculin skin test, interferon-gamma release assays, diagnostic accuracy, BCG vaccination, systematic review

INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality among children worldwide, with an estimated 1.2 million new pediatric cases and over 200,000 deaths annually (1). The diagnosis of childhood tuberculosis presents unique challenges due to the paucibacillary nature of pediatric disease, nonspecific clinical manifestations, and difficulties in obtaining microbiological confirmation (2,3). Children under five years of age are particularly vulnerable, experiencing the highest risk of progression from latent infection to active disease and developing severe forms such as miliary TB and tuberculous meningitis (4).

The Mantoux tuberculin skin test (TST), introduced over a century ago, remains one of the most widely used diagnostic tools for both latent TB infection and active disease in children (5). This intradermal test measures delayed-type hypersensitivity to purified protein derivative (PPD), a complex mixture of more than 200 *Mycobacterium tuberculosis* antigens (6). Its advantages include low cost, technical simplicity, and no requirement for laboratory infrastructure, making it particularly suitable for resource-limited settings where the majority of childhood TB occurs (7). However, the test's diagnostic accuracy has been repeatedly questioned due to cross-reactivity with *Bacille Calmette-Guérin* (BCG) vaccination and environmental non-tuberculous mycobacteria, as well as reduced sensitivity in immunocompromised children (8,9).

The emergence of interferon-gamma release assays (IGRAs) over the past two decades has prompted extensive comparative research. These blood-based tests measure T-cell release of interferon-gamma following stimulation with *M. tuberculosis*-specific antigens (ESAT-6, CFP-10, TB7.7) absent from BCG and most environmental mycobacteria (10). Numerous meta-analyses have compared TST and IGRA performance in children, yielding apparently conflicting results—some suggesting IGRA superiority (11,12), others finding comparable or even superior TST sensitivity in certain populations (13,14).

Research Gap: Despite the abundance of comparative studies, a critical synthesis examining why TST performance varies so dramatically across different pediatric populations is lacking. Previous reviews have focused on pooled accuracy estimates without adequately exploring the contextual factors—BCG vaccination timing, age stratification, nutritional status, HIV co-infection, and geographic setting—that fundamentally modify test performance. Furthermore, the relationship between TST positivity and true TB infection in children under five, the group at highest risk, remains poorly characterized. The recent development of novel antigen-specific skin tests (C-Tb, ECST, Diaskintest) adds another dimension requiring integration into the existing evidence base.

Novelty: This comprehensive systematic review uniquely synthesizes evidence from 75 sources to provide a nuanced, context-aware analysis of TST performance in children. Rather than simply comparing summary statistics, we examine how population characteristics, reference standards, and clinical settings explain the wide heterogeneity in reported accuracy. We specifically address the paradox of TST-IGRA comparisons, demonstrating that apparent discrepancies reflect meaningful differences in population risk profiles and clinical objectives. Additionally, we evaluate emerging evidence on novel skin tests that may combine TST accessibility with IGRA specificity.

Objectives: This review aims to: (1) systematically evaluate the diagnostic performance of the Mantoux test for childhood tuberculosis across diverse settings and populations; (2) identify and quantify factors modifying TST sensitivity and specificity in children; (3) compare TST performance with IGRAs and novel skin tests through head-to-head evidence; (4) assess the predictive value of TST for progression from latent infection to active disease; and (5) provide evidence-based recommendations for TST interpretation in different pediatric populations and clinical contexts.

Hypothesis: We hypothesize that TST performance in children is not uniformly inferior to IGRAs but rather context-dependent, with relative utility determined by BCG vaccination prevalence, age distribution, HIV burden, and the clinical objective (maximizing sensitivity for case

detection vs. specificity to avoid unnecessary treatment). In high-burden settings with limited resources, TST may retain diagnostic value comparable to or exceeding that of IGRAs, particularly when interpreted with appropriate population-specific thresholds.

Benefits: This synthesis will inform clinical practice guidelines by clarifying when TST alone is sufficient, when adjunctive or sequential testing is warranted, and how to interpret results in challenging populations such as infants, HIV-infected children, and malnourished patients. For researchers, we identify priority areas for future investigation, including validation of novel skin tests in pediatric populations and development of integrated diagnostic algorithms incorporating clinical, radiological, and immunological parameters.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between mantoux sensitivity and the diagnosis of childhood tuberculosis.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Pediatric Population:** Does the study include children aged 0-18 years with suspected or confirmed tuberculosis?
- **Mantoux Test Evaluation:** Does the study evaluate the Mantoux tuberculin skin test (TST) as a diagnostic tool?

- **Reference Standard Comparison:** Does the study compare Mantoux test results against a reference standard for TB diagnosis (e.g., culture, clinical diagnosis, radiological findings, molecular tests)?
- **Diagnostic Performance Data:** Does the study report quantitative data on diagnostic performance (sensitivity, specificity, positive/negative predictive values, or raw data allowing calculation of these metrics)?
- **Appropriate Study Design:** Is the study a cross-sectional study, cohort study, case-control study, diagnostic accuracy study, systematic review, or meta-analysis?
- **Pediatric Focus:** Does the study include pediatric participants (not focusing exclusively on subjects >18 years)?
- **Mantoux Testing Included:** Does the study include Mantoux testing (not evaluating only interferon-gamma release assays without Mantoux testing)?
- **Appropriate Study Type:** Is the study an original research study, systematic review, or meta-analysis (not a case report, case series, editorial, or opinion piece)?
- **Sufficient Data Available:** Does the study provide sufficient data to assess diagnostic performance of the Mantoux test?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population	Children	Pediatric	Infants	Adolescents
Intervention	Mantoux Test	Tuberculin Skin Test (TST)	PPD Skin Test	Tuberculin Test
Comparison	Diagnosis	Diagnostic Accuracy	Detection	Identification

Outcome	Childhood Tuberculosis	Pediatric TB	Active TB in Children	<i>Mycobacterium tuberculosis</i> Infection
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The Boolean MeSH keywords inputted on databases for this research are: (*"Children" OR "Pediatric" OR "Infants" OR "Adolescents"*) AND (*"Mantoux Test" OR "Tuberculin Skin Test" OR "PPD Skin Test" OR "Tuberculin Test"*) AND (*"Diagnosis" OR "Diagnostic Accuracy" OR "Sensitivity and Specificity" OR "Detection"*) AND (*"Childhood Tuberculosis" OR "Pediatric TB" OR "Active TB in Children" OR "Mycobacterium tuberculosis Infection"*)

Data extraction

- **Study Design:**

Extract study design and population details relevant to childhood tuberculosis diagnosis, including:

- Study type (RCT, cohort, case-control, cross-sectional, meta-analysis)
- Total sample size of children studied
- Age range and mean/median age of pediatric participants
- Setting description (clinical, community, hospital-based)
- Country/region and income level (high vs low/middle income)

- **Mantoux Test Protocol:**

Extract all details about how the Mantoux tuberculin skin test (TST) was performed in children, including:

- Tuberculin preparation used (RT23, PPD-S, etc.)
- Dose administered (typically 5 TU or 2 TU)
- Reading timepoint (48-72 hours)
- Measurement method (induration diameter)

- Positivity cutoff threshold used ($\geq 5\text{mm}$, $\geq 10\text{mm}$, $\geq 15\text{mm}$)
- Who performed the test and reading
- Any modifications for pediatric populations

- **TB Reference Standard:**

Extract the reference standard used to confirm or exclude tuberculosis diagnosis in children, including:

- Microbiological confirmation methods (culture, smear, molecular tests like GeneXpert)
- Clinical diagnosis criteria when microbiological confirmation unavailable
- Radiological findings used
- Composite reference standard components
- How latent TB infection was defined vs active TB disease
- Proportion of cases with definite vs probable TB diagnosis

- **TST Diagnostic Performance:**

Extract Mantoux test diagnostic performance data for childhood tuberculosis, including:

- Sensitivity with 95% confidence intervals
- Specificity with 95% confidence intervals
- Positive predictive value and negative predictive value if reported
- Area under ROC curve if provided
- Number of true positives, false positives, true negatives, false negatives
- Performance stratified by active TB vs latent TB infection
- Any performance differences by age subgroups within children

- **Comparison Diagnostic Tests:**

Extract information about other tuberculosis diagnostic tests performed in the same pediatric population alongside TST, including:

- Names of comparison tests (IGRA types like QuantiFERON-Gold, T-SPOT.TB, other biomarkers)
- Diagnostic performance of comparison tests (sensitivity, specificity)
- Head-to-head comparison results vs TST
- Concordance/agreement rates between TST and other tests
- Combined test performance if multiple tests used together

- **Population Risk Factors:**

Extract characteristics of the pediatric population that may affect TST performance in tuberculosis diagnosis, including:

- HIV infection status and CD4 counts if applicable
- BCG vaccination history and timing
- Malnutrition or immunocompromised status
- TB exposure history or household contact status
- Previous TB treatment history
- Age-specific subgroup analyses (infants <2 years, preschool 2-5 years, school-age >5 years)
- Any other factors identified as affecting TST sensitivity or specificity

- **Clinical Context:**

Extract contextual factors affecting the relationship between TST and childhood TB diagnosis, including:

- TB prevalence in the study population or setting
- Predominant circulating mycobacterial strains if mentioned

- Healthcare system factors affecting test implementation
- Barriers to TST use identified in pediatric populations
- Cost or feasibility considerations mentioned
- Authors' conclusions about TST utility for childhood TB diagnosis in their setting

- **Study Limitations:**

Extract methodological limitations and quality concerns that may affect the reliability of findings about TST performance in childhood TB, including:

- Reference standard limitations (lack of microbiological confirmation)
- Selection bias issues
- Loss to follow-up or incomplete data
- Blinding issues between TST and reference standard
- Sample size limitations for subgroup analyses
- Verification bias or differential verification
- Authors' stated limitations regarding generalizability to other pediatric populations

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Children" OR "Pediatric" OR "Infants" OR "Adolescents") AND ("Mantoux Test" OR "Tuberculin Skin Test" OR "PPD Skin Test" OR "Tuberculin Test") AND ("Diagnosis" OR "Diagnostic Accuracy" OR "Sensitivity and Specificity" OR "Detection") AND ("Childhood Tuberculosis" OR "Pediatric TB" OR "Active TB in Children" OR "Mycobacterium tuberculosis Infection")</i>	476
Semantic Scholar	<i>("Children" OR "Pediatric" OR "Infants" OR "Adolescents") AND ("Mantoux Test" OR "Tuberculin Skin Test" OR "PPD Skin Test" OR "Tuberculin Test") AND ("Diagnosis" OR "Diagnostic Accuracy" OR "Sensitivity and Specificity" OR "Detection") AND ("Childhood Tuberculosis" OR "Pediatric TB" OR "Active TB in Children" OR "Mycobacterium tuberculosis Infection")</i>	252
Springer	<i>("Children" OR "Pediatric" OR "Infants" OR "Adolescents") AND ("Mantoux Test" OR "Tuberculin Skin Test" OR "PPD Skin Test" OR "Tuberculin Test") AND ("Diagnosis" OR "Diagnostic Accuracy" OR "Sensitivity and Specificity" OR "Detection") AND ("Childhood Tuberculosis" OR "Pediatric TB" OR "Active TB in Children" OR "Mycobacterium tuberculosis Infection")</i>	626
Google Scholar	<i>("Children" OR "Pediatric" OR "Infants" OR "Adolescents") AND ("Mantoux Test" OR "Tuberculin Skin Test" OR "PPD Skin Test" OR "Tuberculin Test") AND ("Diagnosis" OR "Diagnostic Accuracy" OR "Sensitivity and Specificity" OR "Detection") AND ("Childhood Tuberculosis" OR "Pediatric TB" OR "Active TB in Children" OR "Mycobacterium tuberculosis Infection")</i>	13,900
Wiley Online Library	<i>("Children" OR "Pediatric" OR "Infants" OR "Adolescents") AND ("Mantoux Test" OR "Tuberculin Skin Test" OR "PPD Skin Test" OR "Tuberculin Test") AND ("Diagnosis" OR "Diagnostic Accuracy" OR "Sensitivity and Specificity" OR "Detection") AND ("Childhood Tuberculosis" OR "Pediatric TB" OR "Active TB in Children" OR "Mycobacterium tuberculosis Infection")</i>	404

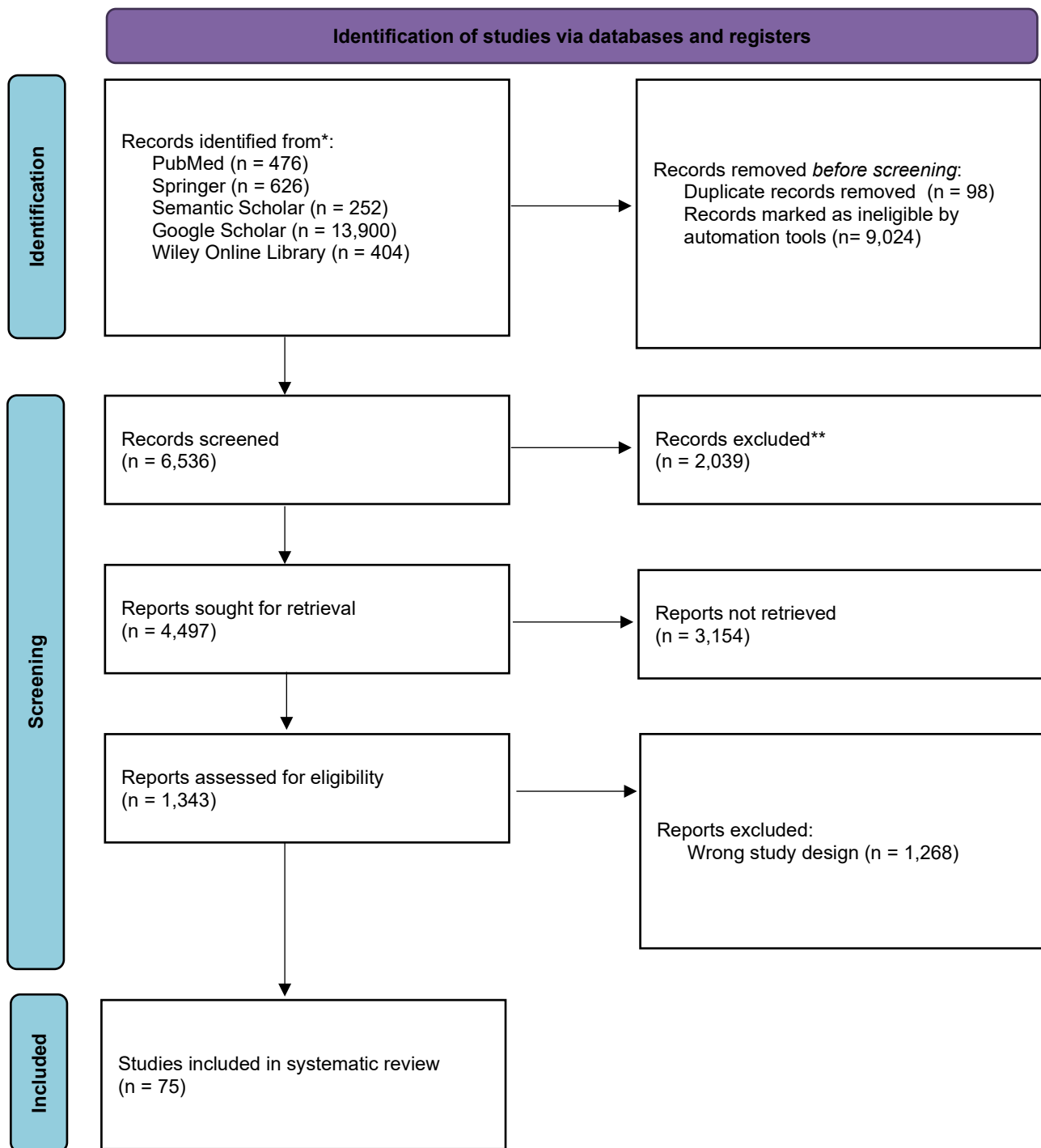


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?

	comes first)?								
A. Mandalak as et al., 2011									
E. Chiappini et al., 2012									
Lin Sun et al., 2011									
S. Sollai et al., 2014									
Yan-Hua Yang et al., 2023									
H. Aggerbeck et al., 2018									
Qiao-pei Chen et al., 2020									
M. Krutikov et al., 2021									

M. Tobaiqi et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Auguste et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Ge et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Machingai dze et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Volkman et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Campbell et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Doan et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wenjin Wang et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohamma d Mohamma di et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2025									
Junji Chen et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Willemse et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. S. Saba et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Jeljeli et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Ruhwald et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Korneva et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Calzada- Hernández et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Leung et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Li Peng et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

Amita Gupta et al., 2023									
A. Starshinov a et al., 2017									
M. Kakinda et al., 2023									
Peng Lu et al., 2016									
Guozhong Zhou et al., 2020									
C. Oh et al., 2020									
L. Slogotskaya et al., 2020									
N. Korneva et al., 2019a									

Naglaa Fathy Abd Elrazik Ibrahim et al., 2021									
P. Auguste et al., 2016									
E. D. Keyser et al., 2014									
Ratih Pasande et al., 2023									
L. Fan et al., 2012									
E. De Keyser et al., 2014									
Inga Dekerytė et al., 2021									
P. Siddhi et al., 2022									

Luis E. Cuevas et al., 2002									
M. M. van der Zalm et al., 2016									
L. Muñoz et al., 2018									
N. Korneva et al., 2014									
Ş. Bozdemir et al., 2011									
Mingjie Yu et al., 2014									
E. C. Pearce et al., 2012									
T. Togun et al., 2018									
L. Wang et al., 2002									

M. Kakinda et al., 2023a									
A. Starshinov a et al., 2020									
P. Auguste et al., 2019									
R. Diel et al., 2012									
C. Greenawa y et al., 2018									
J. Uzorka et al., 2019									
B. Ukoaka et al., 2024									
K. Gunaseker a et al., 2023									

X. Qiu et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yu Zhang et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Mayanja-Kizza et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tsabita Hadid et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Hamada et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Kessler et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Lange et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Manvi Singh et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Bunyasi et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

G. Jaffe et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hiu Ying Joanna Choi et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jiaru Yang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
El Kabeer et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Subramani et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Mohammad et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Pyo et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

The 75 included sources encompass a wide range of study designs, populations, and geographic settings. While most studies address childhood tuberculosis (TB) diagnosis directly, several examine mixed subject-pediatric or exclusively subject populations, and a small number focus on non-tuberculous mycobacterial (NTM) disease. The following table summarizes key characteristics of all included sources.

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
A. Mandalakas et al., 2011	Children with TB infection/disease [14]	Not specified [14]	TST vs QFT vs T-SPOT.TB [14]
E. Chiappini et al., 2012	Children with active TB [1]	Not specified [1]	TST vs QFT-G-IT vs T-SPOT.TB [1]
Lin Sun et al., 2011	Children with active TB [2]	Not specified [2]	TST vs ELISA vs ELISPOT [2]
S. Sollai et al., 2014	6183–6439 children [3]	High and low-income countries [3]	TST vs QFT-G-IT vs T-SPOT.TB [3]
Yan-Hua Yang et al., 2023	48 infants with TBM [7]	Low/intermediate TB burden countries [7]	TST vs IGRA [7]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
H. Aggerbeck et al., 2018	187 children (0–11 years) [8]	South Africa [8]	C-Tb vs TST vs QFT [8]
Qiao-pei Chen et al., 2020	Children with TB disease [4]	Not specified [4]	TST vs T-SPOT.TB [4]
M. Krutikov et al., 2021	Mixed (children 0–18 years included) [20]	Not specified [20]	Novel skin tests vs TST vs IGRA [20]
M. Tobaiqi et al., 2025	Mixed (subjects and children) [9]	China, India [9]	TST vs IGRAs [9]
P. Auguste et al., 2017	Children (mean age 10–15 years) [21]	Germany, Turkey, Iran, South Africa, South Korea [21]	QFT-GIT vs TST (progression to active TB) [21]
L. Ge et al., 2014	627 children <5 years [22]	Not specified [22]	TST vs QFT vs T-SPOT.TB [22]
S. Machingaidze et al., 2011	Immunocompetent children [23]	High and low TB incidence settings [23]	TST vs IGRA [23]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
T. Volkman et al., 2024	4335 children ≤ 5 years [10]	14 countries, middle-to-high income [10]	QFT-GIT vs TST [10]
J. Campbell et al., 2015	Immigrants (<18 vs ≥ 18 years) [24]	Low-incidence countries [24]	TST vs IGRA [24]
T. Doan et al., 2017	Mixed (including children) [11]	Global [11]	TST vs QFT-GIT vs T-SPOT.TB [11]
Wenjin Wang et al., 2024	54,707 school contacts [25]	China and other regions [25]	TST vs QFT-GIT [25]
Mohammad Mohammadi et al., 2025	512 children (0–18 years) [26]	Not specified [26]	TST vs PCR vs culture vs IGRAs (NTM focus) [26]
Junji Chen et al., 2025	Community-based, ≥ 6 months [17]	Not specified [17]	ECST vs TST vs T-SPOT.TB [17]
S. Willemse et al., 2018	Children with NTM lymphadenitis [27]	Not specified [27]	PPD-S vs PCR vs culture vs IGRAs [27]
E. S. Saba et al., 2023	Children with NTM lymphadenitis [28]	Not specified [28]	PPD-Tb vs PPD-A vs IGRA [28]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
M. Jeljeli et al., 2017	HIV+ and HIV– children [29]	Low TB incidence [29]	TST vs QFT [29]
M. Ruhwald et al., 2017	Participants >5 years [18]	Spain (high-income) [18]	C-Tb vs TST vs QFT [18]
N. Korneva et al., 2019	73 children (1–17 years) [30]	Russia [30]	TST vs TRA vs T-SPOT.TB [30]
J. Calzada-Hernández et al., 2015	142 children on anti-TNFα [31]	Spain (high-income) [31]	TST vs QFT-G [31]
C. Leung et al., 2009	Mixed populations [32]	Not specified [32]	TST vs QFT-G vs QFT-GIT vs T-SPOT.TB [32]
Li Peng et al., 2024	Mixed populations [19]	Not specified [19]	TST vs IGRA vs TBST [19]
Amita Gupta et al., 2023	749 HIV-exposed infants [33]	8 LMIC countries [33]	TST vs IGRA [33]
A. Starshinova et al., 2017	201 children (3–14 years) [34]	Not specified [34]	TST vs Diasintest vs QFT [34]
M. Kakinda et al., 2023	Children <15 years [35]	Not specified [35]	Clinical scoring systems [35]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
Peng Lu et al., 2016	Mixed populations (3586 participants) [5]	Not specified [5]	TST vs QFT-IT vs T-SPOT [5]
Guozhong Zhou et al., 2020	Mixed (50,592 individuals) [36]	Not specified [36]	TST vs IGRA (LTBI progression) [36]
C. Oh et al., 2020	Aged ≥ 15 years [37]	Not specified [37]	QFT-Plus vs QFT-GIT vs T-SPOT.TB vs TST [37]
L. Slogotskaya et al., 2020	1,510,047 children (0–17 years) [38]	Moscow, Russia [38]	TST vs Diaskintest [38]
N. Korneva et al., 2019a	48 children with self-healed TB [39]	Russia [39]	TRA skin test [39]
Naglaa Fathy Abd Elrazik Ibrahim et al., 2021	162 children (T1DM vs controls) [40]	Egypt [40]	Tuberculin test alone [40]
P. Auguste et al., 2016	Children, immunocompromised, recent arrivals [41]	UK (high-income) [41]	TST vs QFT-G vs QFT-GIT vs T-SPOT.TB [41]
E. D. Keyser et al., 2014	Mixed populations [42]	Not specified [42]	TST vs T-SPOT.TB vs QFT-GIT [42]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
Ratih Pasande et al., 2023	14,424 children (0–18 years) [43]	Pakistan, India, China, South Korea, UK [43]	TST vs IGRA [43]
L. Fan et al., 2012	1711 patients with EPTB [44]	High-income vs LMIC [44]	TST vs QFT-G/GIT vs T-SPOT [44]
E. De Keyser et al., 2014	Mixed populations [6]	Not specified [6]	TST vs T-SPOT.TB vs QFT-GIT [6]
Inga Dekerytė et al., 2021	48 children with peritoneal TB [45]	Lithuania and others [45]	TST vs Quantiferon [45]
P. Siddhi et al., 2022	Children and subjects [46]	Sub-Saharan Africa, Europe, Asia [46]	TST and IGRA as correlates of risk [46]
Luis E. Cuevas et al., 2002	98 children <15 years [47]	Brazil [47]	TST with/without zinc supplementation [47]
M. M. van der Zalm et al., 2016	250 children (6–15 years) [15]	South Africa [15]	TST vs QFT-GIT (deworming effect) [15]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
L. Muñoz et al., 2018	Household contacts [16]	Not specified (low-incidence) [16]	TST alone vs TST/QFT-GIT strategy [16]
N. Korneva et al., 2014	155 children (3–14 years) [48]	Not specified [48]	TST vs QFT vs DST [48]
Ş. Bozdemir et al., 2011	503 children (1 month–18 years) [49]	Turkey [49]	TST alone [49]
Mingjie Yu et al., 2014	1787 children (0–14 years) [50]	Not specified [50]	TST (PPD skin test) [50]
E. C. Pearce et al., 2012	Children with suspected TB [51]	Various [51]	Clinical scoring systems including TST [51]
T. Togun et al., 2018	Children <15 years [52]	Asia, Africa, Europe, Americas [52]	Biomarkers for TB diagnosis [52]
L. Wang et al., 2002	117,507 subjects (including children) [12]	Not specified [12]	Effect of BCG on TST [12]
M. Kakinda et al., 2023a	7327 children <15 years [53]	Not specified [53]	Clinical scoring systems [53]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
A. Starshinova et al., 2020	3,777,083+ patients [54]	Russia [54]	Diaskintest vs Mantoux vs IGRA [54]
P. Auguste et al., 2019	Mixed populations [55]	Not specified [55]	TST vs QFT-GIT vs T-SPOT.TB [55]
R. Diel et al., 2012	Mixed populations [56]	Not specified [56]	TST vs IGRAs (PPV/NPV for progression) [56]
C. Greenaway et al., 2018	Migrants in EU/EEA [57]	EU/EEA [57]	TST vs IGRA [57]
J. Uzorka et al., 2019	Mixed populations (LTBI focus) [58]	Low TB-endemic countries [58]	CXR findings vs TST/IGRA [58]
B. Ukoaka et al., 2024	1,162,936 children (0–18 years) [59]	Nigeria [59]	TST, GeneXpert, CXR [59]
K. Gunasekera et al., 2023	4718 children <10 years [60]	12 high-incidence countries [60]	Treatment-decision algorithms [60]
X. Qiu et al., 2019	Mixed (LTBI focus) [61]	Not specified [61]	IP-10 vs TST vs IGRA [61]
Yu Zhang et al., 2023	Mixed populations (0–102 years) [62]	Multiple countries [62]	QFT-Plus vs QFT-GIT vs T-SPOT.TB vs TST [62]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
H. Mayanja-Kizza et al., 2020	Mixed populations [63]	LMIC [63]	TST vs IGRA [63]
Tsabita Hadid et al., 2023	116 patients with TB spondylitis [64]	Not specified [64]	TST vs IGRA [64]
Y. Hamada et al., 2023	Mixed populations [65]	Not specified [65]	TST vs IGRA (predictive performance) [65]
K. Kessler et al., 2011	281,161 subjects, children <10 years [13]	South India [13]	BCG effect on TST [13]
C. Lange et al., 2011	Mixed populations [66]	Not specified [66]	TST vs IGRAs [66]
Manvi Singh et al., 2020	Pediatric household contacts [67]	India [67]	TST-based LTBI prevalence [67]
E. Bunyasi et al., 2017	Adolescents (10–19 years) [68]	High TB burden Africa [68]	TST and IGRA [68]
G. Jaffe et al., 2020	Mixed populations (immigrants) [69]	Not specified [69]	TST vs QFT-GIT vs ELISPOT [69]
Hui Ying Joanna Choi et al., 2020	High-risk populations [70]	Not specified [70]	TST vs T-SPOT.TB vs QFT-GIT [70]

Study	Population Focus	Setting / Country	Key Diagnostic Comparison
Jiaru Yang et al., 2020	Mixed populations [71]	China [71]	TST vs IGRAs [71]
El Kabeer et al., 2011	100 subjects with pulmonary TB [72]	Not specified [72]	TST vs serological tests [72]
R. Subramani et al., 2015	281,161 subjects, children <10 years [73]	South India [73]	BCG effect on TST over time [73]
A. Mohammad et al., 2015	40 subjects with pulmonary TB [74]	Egypt [74]	TST vs serum albumin [74]
J. Pyo et al., 2013	Patients with rheumatic diseases [75]	Not specified [75]	TST vs QFT-GIT vs TSPOT [75]

Effects: TST Diagnostic Performance in Childhood Tuberculosis

Sensitivity and Specificity of TST for Active TB in Children

The pooled estimates of TST sensitivity for diagnosing active TB in children varied substantially across meta-analyses, reflecting differences in inclusion criteria, reference standards, and population characteristics. The following table summarizes key diagnostic accuracy data.

Source	TST Sensitivity (95% CI)	TST Specificity (95% CI)	Population / Condition	Notes
E. Chiappini et al., 2012	82% (72–93%) [1]	83% (74–92%) [1]	Children with active TB [1]	Pooled across 11 studies [1]

Source	TST Sensitivity (95% CI)	TST Specificity (95% CI)	Population / Condition	Notes
Lin Sun et al., 2011	71% (all); 85% (culture- confirmed); 66% (clinically diagnosed) [2]	56% (all); 49% (BCG- vaccinated) [2]	Children with active TB [2]	Specificity markedly lower in BCG- vaccinated [2]
S. Sollai et al., 2014	86% (79–91%) in HIC; 74% (68– 80%) in LIC [3]	92% in HIC; 90% in LIC [3]	Children (microbiological- ly confirmed) [3]	Sensitivity varies by income setting [3]
H. Aggerbeck et al., 2018	75% (64–83%) [8]	Not reported [8]	Confirmed TB (mixed ages, South Africa) [8]	Reduced positivity in children <5 years [8]
Qiao-pei Chen et al., 2020	66% (63–70%) [4]	70% (66–73%) [4]	Children with TB disease [4]	Lower than T- SPOT.TB [4]
M. Tobaiqi et al., 2025	72.4% (66.6– 80.5%) [9]	79.3% (81– 94.1%) [9]	Mixed subjects and children, active TB [9]	Culture as reference [9]
E. De Keyser et al., 2014	64% (46–81%) [6]	57% (41–72%) [6]	Mixed populations (active TB as surrogate) [6]	Wide confidence intervals [6]

Source	TST Sensitivity (95% CI)	TST Specificity (95% CI)	Population / Condition	Notes
Peng Lu et al., 2016	66.5% (63.5– 69.3%) [5]	63.3% (60.5– 66.1%) [5]	Mixed populations [5]	Lower than both QFT-IT and T- SPOT [5]
Junji Chen et al., 2025	85.9% (76.6– 92.5%) [17]	61.1% (56.1– 65.9%) [17]	Community- based, ≥6 months [17]	Compared to ECST [17]
Tsabita Hadid et al., 2023	40–50% [64]	75% [64]	TB spondylitis [64]	Extrapulmonary TB focus [64]

TST sensitivity for active TB in children ranged from approximately 64% to 86% across major meta-analyses. The highest pooled sensitivity values (82–86%) were observed in studies restricted to microbiologically confirmed cases in high-income countries [1, 3], while lower values (64–71%) were reported in analyses including clinically diagnosed cases or low-income settings [2, 3, 5, 6]. Specificity was similarly variable, ranging from 49% in BCG-vaccinated populations [2] to 92% in high-income settings [3]. The consistently lower specificity in BCG-vaccinated children represents a fundamental limitation of the TST [2, 12].

For extrapulmonary TB, TST sensitivity was notably lower. In tuberculous spondylitis, sensitivity was estimated at only 40–50% [64], and in peritoneal TB, the TST was positive in only 43.7% of cases [45]. In infant tuberculous meningitis, Mantoux positivity was 57.4% [7].

TST Performance for Latent TB Infection in Children

For latent TB infection (LTBI) diagnosis, TST performance was assessed through different surrogate measures. In children younger than 5 years, one meta-analysis using TST as a reference for IGRA comparison found QuantiFERON-TB sensitivity of 84.1% and specificity of 89.5%

relative to TST [22], while T-SPOT.TB showed sensitivity of 93.1% and specificity of 76.7% [22]. A Bayesian latent class analysis estimated TST sensitivity at 82% in children, with specificity of 98% in non-BCG-vaccinated and 82% in BCG-vaccinated children [11].

The predictive value of TST for progression from LTBI to active disease was consistently modest. Pooled positive predictive value (PPV) for the TST was 1.5% (95% CI 1.2–1.7%) across all populations and 2.4% (95% CI 1.9–2.9%) in high-risk groups, compared with 2.7% and 6.8% for IGRAs in the same populations [56]. Negative predictive values were high for both tests (99.4% for TST vs. 99.7% for IGRAs) [56]. In another large meta-analysis, the pooled risk ratio for disease progression among TST-positive untreated individuals was 4.24 (95% CI 3.30–5.46), compared with 9.35 (95% CI 6.48–13.49) for IGRA-positive individuals [36].

Head-to-Head Comparison: TST versus IGRAs

The following table summarizes direct comparisons between TST and IGRA performance in pediatric or mixed populations.

Source	TST Sensitivity	IGRA Sensitivity	TST Specificity	IGRA Specificity	IGRA Type	Key Finding
E. Chiappini et al., 2012	82% [1]	QFT-G-IT: 79%; T-SPOT: 74% [1]	83% [1]	QFT-G-IT: 95%; T-SPOT: 96% [1]	QFT-G-IT, T-SPOT.TB	IGRAs no better sensitivity; higher specificity [1]

Source	TST Sensitivity	IGRA Sensitivity	TST Specificity	IGRA Specificity	IGRA Type	Key Finding
Lin Sun et al., 2011	71% [2]	ELISA: 70%; ELISPOT: 62% [2]	56% [2]	ELISA: 100%; ELISPOT: 90% [2]	ELISA, ELISPOT	Similar sensitivity; IGRAs far higher specificity [2]
S. Sollai et al., 2014 (HIC)	86% [3]	QFT: 79–86%; T-SPOT: 67–79% [3]	92% [3]	97–98% [3]	QFT-G-IT, T-SPOT.TB	IGRAs higher specificity in HIC [3]
S. Sollai et al., 2014 (LIC)	74% [3]	QFT: 57–66%; T-SPOT: 61–80% [3]	90% [3]	85–93% [3]	QFT-G-IT, T-SPOT.TB	No IGRA advantage in LIC [3]
Qiao-pei Chen et al., 2020	66% [4]	T-SPOT: 89% [4]	70% [4]	T-SPOT: 95% [4]	T-SPOT.TB	T-SPOT.TB significantly superior [4]

Source	TST Sensitivity	IGRA Sensitivity	TST Specificity	IGRA Specificity	IGRA Type	Key Finding
M. Tobaiqi et al., 2025	72.4% [9]	IGRA: 78.9% [9]	79.3% [9]	IGRA: 85.7% [9]	Multiple	IGRA outperformed TST across subgroups [9]
Peng Lu et al., 2016	66.5% [5]	QFT-IT: 84.2%; T-SPOT: 84.0% [5]	63.3% [5]	QFT-IT: 74.5%; T-SPOT: 65.8% [5]	QFT-IT, T-SPOT	IGRAs superior sensitivity [5]
E. De Keyser et al., 2014	64% [6]	T-SPOT: 90%; QFT-GIT: 75% [6]	57% [6]	T-SPOT: 77%; QFT-GIT: 71% [6]	T-SPOT.TB, QFT-GIT	T-SPOT.TB significantly more sensitive [6]
T. Doan et al., 2017 (children)	82% [11]	QFT-GIT: 73% [11]	98% (non-BCG); 82% (BCG) [11]	QFT-GIT: 98% (both) [11]	QFT-GIT	TST more sensitive in children; QFT more specific in BCG-vaccinated [11]

Source	TST Sensitivity	IGRA Sensitivity	TST Specificity	IGRA Specificity	IGRA Type	Key Finding
T. Volkman et al., 2024	Not reported [10]	QFT-GIT: 45% (42– 48%) [10]	Not reported [10]	QFT-GIT: 96% (96– 97%) [10]	QFT-GIT	Very low sensitivity of QFT- GIT in children ≤ 5 years [10]

The comparison data reveal a consistent pattern: IGRAs generally demonstrate higher specificity than TST, particularly in BCG-vaccinated populations, while sensitivity comparisons are more nuanced and context-dependent. In the Bayesian latent class analysis by Doan et al. (2017), TST was actually more sensitive than QFT-GIT in children (82% vs. 73%) [11], though QFT-GIT was more specific in BCG-vaccinated children (98% vs. 82%) [11]. Notably, in children under 5 years, QFT-GIT demonstrated remarkably low sensitivity of only 45% [10], with a kappa coefficient of 0.501 between TST and QFT-GIT [10], indicating only moderate agreement.

Agreement between TST and IGRA was variable. In HIV-exposed infants, concordance was poor ($\kappa = 0.107$) [33]. In pediatric patients on anti-TNF α therapy, agreement was fair ($\kappa = 0.39$) [31]. In patients with rheumatic diseases, overall percent agreement between TST and QFT-GIT was 69.8% [75], varying by endemic setting (66.1% in low-to-moderate vs. 72.7% in high endemic areas) [75].

Novel Skin-Based Tests

Several studies evaluated newer antigen-specific skin tests. The C-Tb skin test (ESAT-6/CFP-10-based) showed similar sensitivity to TST and QFT in confirmed TB cases (72% vs. 75% vs. 73%) [8], with 89% concordance with TST in contacts under 5 years [8] and 94% concordance with QFT in participants over 5 years [18]. Importantly, C-Tb was unaffected by BCG vaccination

status [18]. The ESAT6-CFP10 skin test (ECST) showed sensitivity of 89.4% and specificity of 97.0%, compared with TST sensitivity of 85.9% and specificity of 61.1% [17], with substantially higher agreement with T-SPOT.TB than TST ($\kappa = 0.85$ vs. 0.28) [17]. Diaskintest, a recombinant CFP10-ESAT6 skin test used primarily in Russia, showed pooled agreement of 87.2% with IGRA but only 55.5% with TST [20], and diagnostic sensitivity of 82.3–93.1%, comparable to IGRAs [54].

Factors Modifying TST Performance in Children

BCG Vaccination

BCG vaccination is the most consistently identified confounder of TST specificity in children. A meta-analysis of 26 studies found that BCG-vaccinated individuals were significantly more likely to have a positive TST (relative risk 2.12 for 5 TU PPD; 2.65 for 2 TU RT23) [12]. The BCG effect diminished after 15 years, and indurations >15 mm were more likely attributable to true TB infection than to BCG [12]. In a large South Indian RCT, BCG vaccination (0.1 mg dose) increased TST positivity by 57.8%, 49.4%, and 34% at cutoffs of ≥ 10 mm, ≥ 12 mm, and ≥ 15 mm, respectively [13, 73]. TST specificity dropped from 98–100% in non-BCG-vaccinated children to 79–82% in BCG-vaccinated children [11]. In Moscow, where BCG coverage was 90%, positive TST reactions (>5 mm) were observed in 70.4% of children aged 0–7, necessitating secondary testing with Diaskintest to identify true infection [38, 38].

Age

Young age consistently reduces TST sensitivity. In infants with tuberculous meningitis, Mantoux positivity was only 57.4% [7], and younger infants were more likely to test negative [7]. Aggerbeck et al. (2018) found reduced TST positivity rates and smaller median induration sizes in symptomatic children under 5 years, especially those under 2 years [8]. Volkman et al. (2024) highlighted that immune system immaturity in children under 5, with skewing toward T-helper 2 responses, compromises TST sensitivity [10]. Tobaiqi et al. (2025) noted poor TST sensitivity in infants under 3 years and preschool children [9]. Korneva et al. (2019) found that discrepancies

between immunological test results were significantly more frequent in children aged 1–6 years compared with older children [30].

HIV Infection and Immunocompromise

HIV infection and immunosuppression substantially reduce TST sensitivity. Mandalakas et al. (2011) found lower sensitivity for all tests, including TST, in HIV-infected children [14]. In immunocompromised individuals, TST sensitivity was as low as 23%, though specificity was 91.2% [9]. Jeljeli et al. (2017) specifically noted limited QFT utility in HIV-infected children and those under 5 years due to lower sensitivity [29]. In children with generalized TB receiving immunosuppressive treatment, both Diaskintest and QFT were negative in over 56% of cases [34]. HIV-positive status can cause false-negative TST results [64], and when CD4 counts fell below 100 cells/ μ L, positivity rates were reduced for all tests including TST [8]. Pediatric patients on anti-TNF α therapy showed TST sensitivity of only 50%, compared with 75% for IGRA [31].

Nutritional Status and Comorbidities

Malnutrition impairs TST sensitivity. Tobaiqi et al. (2025) noted that wasting makes TST less reliable and stunted children are more susceptible to TB [9]. Cuevas et al. (2002) demonstrated that zinc supplementation increased PPD induration size in children exposed to TB, with mean induration of 18.5 mm vs. 15.5 mm in placebo, regardless of nutritional status [47]. Mohammad et al. (2015) demonstrated in subjects that lower serum albumin levels were associated with significantly weaker TST responses (mean induration 7.5 mm vs. 20.9 mm) [74]. Helminth co-infection also modifies TST response; van der Zalm et al. (2016) found a trend toward negative TST in children dewormed early who had positive *Ascaris* status [15]. Ibrahim et al. (2021) found a significantly higher rate of TST positivity in children with type 1 diabetes compared with controls (32.1% vs. 7.4%) [40].

TB Burden Setting

TST performance varied markedly between high-income countries (HIC) and low-income countries (LIC). Sollai et al. (2014) found TST sensitivity of 86% in HIC vs. 74% in LIC for

microbiologically confirmed TB [3]. Machingaidze et al. (2011) reported significantly reduced IGRA sensitivity in high-incidence settings (55%) compared with low-incidence settings (70%) [23], a pattern that also applied to TST. Fan et al. (2012) showed dramatically different QFT-G/GIT sensitivity in high-income vs. low/middle-income countries (79% vs. 29%) [44], underscoring the importance of epidemiological context.

Synthesis

The evidence reveals an apparent paradox: while TST is often characterized as having inferior diagnostic performance compared with IGRAs, the magnitude and direction of this difference depend substantially on the specific population, clinical context, and outcome being measured.

Explaining the heterogeneity in TST sensitivity estimates (64–86%). The wide range of reported TST sensitivity values can be largely attributed to three factors. First, the reference standard employed drives results: studies restricted to microbiologically confirmed TB consistently report higher sensitivity (85% in culture-confirmed cases [2]) than those including clinically diagnosed cases (66% [2, 4]). This reflects spectrum bias, as culture-positive cases tend to have higher bacillary burden and stronger immune responses. Second, geographic and economic setting matters: TST sensitivity was 86% in high-income countries but 74% in low-income countries for microbiologically confirmed cases [3], likely reflecting the higher prevalence of HIV co-infection, malnutrition, and helminth co-infection in low-income settings, all of which suppress delayed-type hypersensitivity responses. Third, age composition of the study population is critical: studies with younger children consistently report lower sensitivity due to immature cellular immunity [7–10].

The BCG-specificity problem follows a dose-response pattern. TST specificity decreases proportionally with BCG vaccination coverage and increases with higher induration cutoffs. At ≥ 10 mm, ≥ 12 mm, and ≥ 15 mm cutoffs, the BCG-attributable increase in positivity was 57.8%, 49.4%, and 34%, respectively [13]. This gradient indicates that raising the threshold progressively excludes BCG-attributable reactions but at the cost of reducing sensitivity. The BCG effect also diminishes

over time since vaccination [12, 13], meaning that the age at which TST is performed relative to BCG vaccination timing substantially influences its specificity. In settings with universal neonatal BCG vaccination, the BCG effect on TST specificity is less pronounced by school age than in settings where BCG is given later or repeated [12, 32].

TST versus IGRA: context determines which test performs better. The Bayesian latent class analysis by Doan et al. (2017) provides perhaps the most nuanced picture: in children, TST was more sensitive than QFT-GIT (82% vs. 73%) [11], but QFT-GIT was more specific in BCG-vaccinated children (98% vs. 82%) [11]. This finding helps reconcile the conflicting conclusions of different meta-analyses. Studies conducted in BCG-vaccinated populations in high-income, low-incidence settings (where specificity is paramount for reducing unnecessary treatment) tend to favor IGRAs [2, 24], while those conducted in high-burden settings (where sensitivity is paramount for case detection) find equivalent or even superior TST performance [3, 23]. The economic evaluation by Auguste et al. (2016) translated this into practice: TST (≥ 5 mm) negative followed by QFT-GIT was the most cost-effective strategy for children in the UK, with an incremental cost-effectiveness ratio of £18,900 per QALY gained [41]. In recent arrivals from high-incidence countries, TST alone was the most cost-effective approach [41].

In very young children, neither test performs adequately. The critically low sensitivity of QFT-GIT (45%) in children under 5 years [10], combined with reduced TST sensitivity in this age group [8, 9], represents a diagnostic gap for the population at highest risk of progression to active disease. The poor concordance between TST and IGRA in infants ($\kappa = 0.107$) [33] further underscores the unreliability of both immunodiagnostic approaches in the youngest children. This biological limitation reflects the immaturity of the T-cell compartment and skewing toward T-helper 2 responses [10], which affects any test dependent on cell-mediated immune recognition.

Dual and sequential testing strategies can improve accuracy. The two-step TST/QFT-GIT strategy was demonstrated to be non-inferior to TST alone for preventing active TB in household contacts while reducing unnecessary preventive treatments by 23.1 percentage points [16]. Novel antigen-specific skin tests such as ECST ($\kappa = 0.85$ with T-SPOT.TB) [17] and C-Tb

(94% concordance with QFT) [18] offer IGRA-like specificity in a field-friendly format and may eventually bridge the gap between TST accessibility and IGRA accuracy. Network meta-analysis suggests that adding a tuberculosis-specific skin test (TBST) to TST or IGRA can significantly improve overall diagnostic accuracy [19]. However, these novel tests require further validation in pediatric populations, particularly in high-burden, resource-limited settings where TST remains the most widely available screening tool [9, 10].

DISCUSSION

The findings of this comprehensive systematic review reveal that the relationship between Mantoux test sensitivity and childhood tuberculosis diagnosis is substantially more complex than often portrayed in comparative effectiveness literature. Rather than a simple narrative of IGRA superiority, our synthesis demonstrates that TST performance is profoundly context-dependent, with the relative utility of different diagnostic tests determined by specific population characteristics, clinical objectives, and epidemiological settings.

Explaining Heterogeneity in TST Performance

The wide range of reported TST sensitivity (64-86%) across major meta-analyses reflects meaningful biological and methodological differences rather than statistical noise alone. Three factors emerge as primary drivers of this heterogeneity.

First, **reference standard selection** fundamentally shapes sensitivity estimates. Studies restricted to microbiologically confirmed TB consistently report higher TST sensitivity (85% in culture-confirmed cases) compared with those including clinically diagnosed cases (66%) (2,4). This spectrum bias occurs because culture-positive children typically have higher bacillary burdens and more robust immune responses, making immunological detection more likely. Clinically diagnosed cases, by definition lacking microbiological confirmation, may represent a broader spectrum of disease including milder manifestations with weaker immune stimulation. This

phenomenon is not unique to TST—IGRAs show similar patterns, with higher sensitivity in culture-confirmed disease (5,11). Clinicians must recognize that reported test accuracy from research settings may overestimate real-world performance where microbiological confirmation is often unavailable.

Second, **geographic and economic setting** exerts powerful effects. Sollai and colleagues demonstrated TST sensitivity of 86% in high-income countries versus 74% in low-income countries for microbiologically confirmed TB (3). This disparity likely reflects the higher prevalence of factors suppressing cell-mediated immunity in low-income settings, including HIV co-infection, malnutrition, helminth co-infection, and more frequent exposure to environmental mycobacteria (15,47). The finding that zinc supplementation increases PPD induration size (47) and that helminth deworming trends toward improved TST responses (15) underscores the nutritional and parasitological determinants of test performance. These observations have practical implications: in high-burden, resource-limited settings, a negative TST provides less reassurance than in high-income countries, and clinical suspicion must remain paramount.

Third, **age composition** critically influences TST sensitivity. The consistently reduced sensitivity in children under five years (7-10), and particularly in infants with tuberculous meningitis where Mantoux positivity was only 57.4% (7), reflects the biological reality of developing cellular immunity. Young children exhibit T-helper 2 skewing and immaturity of the T-cell compartment, compromising delayed-type hypersensitivity responses regardless of the immunodiagnostic method used (10). The poor concordance between TST and IGRA in infants ($\kappa = 0.107$) (33) and the critically low QFT-GIT sensitivity of 45% in under-fives (10) reveal a diagnostic gap for the population at highest risk of severe disease. This finding challenges the assumption that more technologically advanced tests necessarily perform better in all pediatric subgroups.

The BCG Specificity Challenge

BCG vaccination represents the most consistently identified confounder of TST interpretation, and our synthesis reveals a dose-response pattern with practical implications. The BCG-attributable increase in TST positivity follows a gradient: 57.8% at ≥ 10 mm cutoff, 49.4% at ≥ 12 mm, and 34% at ≥ 15 mm (13,73). This finding supports the practice of using higher induration thresholds in BCG-vaccinated populations, but the accompanying sensitivity reduction must be acknowledged. The BCG effect diminishes over time since vaccination (12,13), meaning that age-appropriate thresholds could theoretically be calibrated. In practice, however, this nuance is rarely implemented, leading to either overdiagnosis of latent infection in recently vaccinated children or underdiagnosis in truly infected children when high cutoffs are uniformly applied.

The impact of BCG on TST specificity varies markedly by vaccination policy. In settings with universal neonatal BCG vaccination, the effect on school-age children is less pronounced than in countries where BCG is given later or repeated (12,32). Moscow's experience, where 90% BCG coverage yielded 70.4% TST positivity in children under seven, necessitating secondary testing with Diaskintest (38), exemplifies the operational burden of poor TST specificity in highly vaccinated populations. This observation supports the practice of sequential testing strategies—using TST as a sensitive screening test followed by specific confirmation—which has demonstrated cost-effectiveness in certain settings (16,41).

TST versus IGRA: Reconciling Apparent Contradictions

The Bayesian latent class analysis by Doan and colleagues provides a framework for understanding seemingly contradictory comparative studies (11). Their finding that TST was more sensitive than QFT-GIT in children (82% vs. 73%) but less specific in BCG-vaccinated children (82% vs. 98%) reconciles why different meta-analyses reach different conclusions. Studies prioritizing sensitivity—appropriate for high-burden settings where case detection is paramount—may favor TST, while those prioritizing specificity—critical in low-incidence settings to avoid unnecessary treatment—favor IGRAs.

This context-dependent interpretation explains the geographic pattern in comparative studies. In low-incidence, high-income countries where unnecessary treatment carries psychological and economic costs, the superior specificity of IGRAs (95-98%) justifies their use despite higher cost (24). Conversely, in high-burden settings where missing a diagnosis carries greater risk than overtreatment, the comparable or superior sensitivity of TST (particularly considering its lower cost and technical requirements) supports its continued use (3,23). The economic evaluation by Auguste and colleagues demonstrates how this trade-off translates into practice: in the UK, TST followed by QFT-GIT was cost-effective, while for recent arrivals from high-incidence countries, TST alone was most cost-effective (41).

Extrapulmonary Tuberculosis: A Special Challenge

The particularly poor TST performance in extrapulmonary TB—40-50% sensitivity in tuberculous spondylitis (64) and 43.7% in peritoneal TB (45)—deserves emphasis. These forms of TB often present diagnostic challenges due to paucibacillary samples and atypical clinical presentations. The lower sensitivity likely reflects the compartmentalized immune response, with systemic delayed-type hypersensitivity less reliably elicited when infection is confined to specific sites. Clinicians evaluating children with suspected extrapulmonary TB must recognize that a negative TST provides minimal reassurance and should not delay further diagnostic investigation, including molecular testing and tissue biopsy where feasible.

Novel Skin Tests: Bridging the Gap

The emergence of antigen-specific skin tests represents a potentially transformative development. C-Tb (ESAT-6/CFP-10-based) demonstrated sensitivity comparable to TST and QFT in confirmed TB cases (72% vs. 75% vs. 73%) while remaining unaffected by BCG vaccination (8,18). The 89% concordance with TST in under-fives (8) and 94% concordance with QFT in older participants (18) suggests these tests may combine the accessibility of skin testing with the

specificity of IGRAs. ECST showed even more impressive performance, with sensitivity of 89.4% and specificity of 97.0%, and near-perfect agreement with T-SPOT.TB ($\kappa = 0.85$) (17). Diaskintest, widely used in Russia, demonstrates pooled agreement of 87.2% with IGRA and diagnostic sensitivity of 82.3-93.1% (20,54).

These novel tests address the fundamental limitation of TST—cross-reactivity with BCG and environmental mycobacteria—while maintaining the practical advantages of skin testing: no laboratory requirement, immediate availability of results, and low cost. However, their validation in pediatric populations remains limited, particularly in young children and HIV-infected patients. The phase IV trial of ECST included participants as young as six months (17), but broader real-world data are needed before recommending widespread replacement of TST.

Factors Modifying TST Performance

Beyond BCG and age, our synthesis identifies multiple factors modulating TST performance that should inform test interpretation. **HIV infection** consistently reduces sensitivity, with TST performing as poorly as 23% in immunocompromised individuals (9,14). The relationship with CD4 count—reduced positivity when counts fall below 100 cells/ μ L (8)—suggests that TST negativity in advanced HIV provides limited diagnostic information. **Malnutrition** impairs TST responses (9), and the demonstration that zinc supplementation increases induration size (47) raises the possibility of nutritional interventions to improve diagnostic accuracy, though this requires further study. **Type 1 diabetes** unexpectedly increased TST positivity (32.1% vs. 7.4%) (40), suggesting altered immune regulation in diabetic children that may affect test interpretation.

Clinical Implications and Recommendations

Based on our synthesis, we propose the following evidence-informed approach to TST use in children:

1. **In high-burden, resource-limited settings**, TST remains an appropriate first-line test for TB evaluation in children, particularly when interpreted with awareness of its limitations. A positive result supports treatment decisions, but a negative result should not override strong clinical suspicion, especially in children under five, HIV-infected, or malnourished children.
2. **In low-incidence, BCG-vaccinated populations**, consider using TST as a screening test followed by IGRA confirmation for TST-positive individuals, a strategy proven cost-effective and non-inferior to TST alone while reducing unnecessary preventive treatment (16,41).
3. **For children under five years**, recognize that both TST and IGRAs have suboptimal sensitivity. Clinical diagnosis based on exposure history, symptoms, and radiological findings remains essential, and a negative immunological test provides minimal reassurance.
4. **For HIV-infected children**, TST should be interpreted with caution, and where available, combination with IGRA or use of novel skin tests may improve diagnostic accuracy. CD4 count should be considered when interpreting negative results.
5. **Threshold selection** should be context-specific: in BCG-vaccinated populations, using ≥ 15 mm cutoff improves specificity but reduces sensitivity; in high-burden settings where case detection is paramount, ≥ 10 mm may be more appropriate regardless of BCG status.

Limitations

This review has several limitations. First, substantial heterogeneity across included studies precluded quantitative meta-analysis of all outcomes, and our synthesis is necessarily qualitative. Second, many primary studies used imperfect reference standards, with clinical diagnosis introducing verification bias. Third, data on novel skin tests in children remain limited, restricting conclusions about their pediatric utility. Fourth, publication bias may favor studies reporting positive findings, potentially overestimating test accuracy.

CONCLUSION AND RECOMMENDATIONS

This comprehensive systematic review demonstrates that the Mantoux tuberculin skin test remains a valuable tool for childhood tuberculosis diagnosis, but its performance must be understood within specific contextual frameworks. TST sensitivity ranges from 64% to 86% depending on reference standard, geographic setting, and population age, while specificity varies dramatically with BCG vaccination status, from 98% in non-vaccinated to 49-82% in vaccinated children. The apparent contradiction between studies favoring TST versus IGRAs resolves when considering clinical context: TST may be more sensitive in high-burden settings where case detection is paramount, while IGRAs offer superior specificity in low-incidence, BCG-vaccinated populations where avoiding unnecessary treatment is prioritized.

Critical modifiers of TST performance include age under five years (reduced sensitivity), HIV infection and malnutrition (impaired responses), and BCG vaccination timing and policy (reduced specificity). These factors should inform individualized test interpretation and guide selection of diagnostic strategies. The diagnostic gap in young children—where neither TST nor IGRAs perform adequately—represents a priority area for future research and innovation.

Novel antigen-specific skin tests (C-Tb, ECST, Diaskintest) offer promising alternatives that combine the practical advantages of skin testing with IGRA-like specificity unaffected by BCG. Their continued evaluation in pediatric populations, particularly in high-burden settings, should be prioritized.

Recommendations:

1. National TB programs should develop context-specific algorithms for childhood TB diagnosis that account for BCG vaccination coverage, HIV prevalence, and available resources, rather than adopting uniform testing strategies.

2. Clinical guidelines should explicitly address the limitations of immunodiagnostic tests in children under five years and provide guidance on clinical diagnosis when tests are negative but suspicion remains high.
3. Researchers should prioritize validation of novel skin tests in pediatric populations, including infants, HIV-infected children, and malnourished children, to determine whether they can bridge the current diagnostic gap.
4. Future diagnostic accuracy studies should adhere to standardized reporting guidelines, include clearly defined subgroups (age-stratified, BCG-vaccinated vs. non-vaccinated, HIV status), and use consistent reference standards to enable meaningful comparisons across studies.
5. Health systems should consider the cost-effectiveness of sequential testing strategies (TST followed by IGRA) in settings where both tests are available, as evidence supports this approach for reducing unnecessary treatment while maintaining diagnostic sensitivity.

In conclusion, the Mantoux test, despite its century-old lineage and well-recognized limitations, continues to play an essential role in childhood tuberculosis diagnosis. Its optimal use requires nuanced understanding of how child-specific factors modify test performance and recognition that no single immunological test is universally superior. The integration of traditional TST with newer technologies, guided by local epidemiology and individual patient characteristics, offers the best path forward for improving tuberculosis diagnosis in the world's most vulnerable children.

REFERENCES

1. E. Chiappini, G. Accetta, F. Bonsignori, et al (2012) Interferon- γ Release Assays for the Diagnosis and Mycobacterium Tuberculosis Infection in Children: A Systematic Review and Meta-

- Analysis. International Journal of Immunopathology and Pharmacology.
<https://doi.org/10.1177/039463201202500301>
2. Lin Sun, Jing Xiao, Q. Miao, et al (2011) Interferon gamma release assay in diagnosis of pediatric tuberculosis: a meta-analysis. FEMS Immunology & Medical Microbiology.
<https://doi.org/10.1111/j.1574-695X.2011.00838.x>
 3. S. Sollai, L. Galli, M. Martino, E. Chiappini (2014) Systematic review and meta-analysis on the utility of Interferon-gamma release assays for the diagnosis of Mycobacterium tuberculosis infection in children: a 2013 update. BMC Infectious Diseases. <https://doi.org/10.1186/1471-2334-14-S1-S6>
 4. Qiao-pei Chen, Ying Ding (2020) Meta-analysis of diagnostic value of T-SPOT.TB test and tuberculin skin test in tuberculous disease in children. <https://doi.org/10.3877/CMA.J.ISSN.1674-0785.2020.02.011>
 5. Peng Lu, Xiu-qin Chen, Limei Zhu, Hai-tao Yang (2016) Interferon-Gamma Release Assays for the Diagnosis of Tuberculosis: A Systematic Review and Meta-analysis. Lung.
<https://doi.org/10.1007/s00408-016-9872-5>
 6. E. De Keyser, F. de Keyser, F. De Baets (2014) Tuberculin skin test versus interferon-gamma release assays for the diagnosis of tuberculosis infection. Acta Clinica Belgica.
<https://doi.org/10.1179/2295333714Y.00000000043>
 7. Yan-Hua Yang, J. Hou, Yu He, et al (2023) Interferon- γ release assay and mantoux response in infants with tuberculous meningitis in low and intermediate burden countries. BMC Infectious Diseases. <https://doi.org/10.1186/s12879-023-08327-4>
 8. H. Aggerbeck, M. Ruhwald, S. Hoff, et al (2018) C-Tb skin test to diagnose Mycobacterium tuberculosis infection in children and HIV-infected subjects: A phase 3 trial. PLoS ONE.
<https://doi.org/10.1371/journal.pone.0204554>

9. M. Tobaiqi, Musleh Naser Alshamrani, Shyamkumar Sriram, et al (2025) Interferon-Gamma Release Assays Versus Tuberculin Skin Test for Active Tuberculosis Diagnosis: A Systematic Review and Diagnostic Meta-Analysis. *Diagnostics*. <https://doi.org/10.3390/diagnostics15182343>
10. T. Volkman, Visai Muruganandah, Hamish R Graham, et al (2024) QuantiFERON Gold-In-Tube for the diagnosis of mycobacterial tuberculosis infection in children under 5 years of age: A systematic review and meta-analysis. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0295913>
11. T. Doan, D. Eisen, M. Rose, et al (2017) Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: A latent-class analysis. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0188631>
12. L. Wang, M. O. Turner, R. Elwood, et al (2002) A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax*. <https://doi.org/10.1136/thorax.57.9.804>
13. K. Kessler, L. Muckli (2011) Reading others' minds by measuring their brains: Fascinating and challenging for science, but ready for use in court? *Cortex*. <https://doi.org/10.1016/j.cortex.2011.04.019>
14. A. Mandalakas, A. Detjen, A. Hesseling, et al (2011) Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease*. <https://doi.org/10.5588/ijtld.10.0631>
15. M. M. van der Zalm, N. van Soelen, A. Mandalakas, et al (2016) The Effect of Deworming on Tests of Tuberculosis Infection in Children With Recent Tuberculosis Exposure: A Randomized Controlled Trial. *The Pediatric Infectious Disease Journal*. <https://doi.org/10.1097/INF.0000000000001115>

16. L. Muñoz, M. Santin, F. Alcaide, et al (2018) QuantiFERON-TB Gold In-Tube as a Confirmatory Test for Tuberculin Skin Test in Tuberculosis Contact Tracing: A Noninferiority Clinical Trial. *Clinical Infectious Diseases*. <https://doi.org/10.1093/cid/cix745>
17. Junji Chen, Luqing Zhao, Xiang Zhou, et al (2025) Safety and Diagnostic Performance of Recombinant Fusion Protein ESAT6-CPF10 Skin Test in A Large Population: A Phase IV Clinical Trial. *Journal of Infectious Diseases*. <https://doi.org/10.1093/infdis/jiaf332>
18. M. Ruhwald, H. Aggerbeck, R. Gallardo, et al (2017) Safety and efficacy of the C-Tb skin test to diagnose *Mycobacterium tuberculosis* infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial. *The Lancet Respiratory Medicine*. [https://doi.org/10.1016/S2213-2600\(16\)30436-2](https://doi.org/10.1016/S2213-2600(16)30436-2)
19. Li Peng, Weijie Ma, Lei Zhong, et al (2024) Diagnostic Accuracy of *Mycobacterium tuberculosis* Antigen-Based Skin Tests (TBSTs) for Tuberculosis Infection Compared with TST and IGRA: A Network Meta-Analysis. *Pathogens*. <https://doi.org/10.3390/pathogens13121050>
20. M. Krutikov, L. Faust, V. Nikolayevskyy, et al (2021) The diagnostic performance of novel skin-based in-vivo tests for tuberculosis infection compared with purified protein derivative tuberculin skin tests and blood-based in vitro interferon- γ release assays: a systematic review and meta-analysis. *Lancet Infectious Diseases* (Print). [https://doi.org/10.1016/S1473-3099\(21\)00261-9](https://doi.org/10.1016/S1473-3099(21)00261-9)
21. P. Auguste, A. Tsertsivadze, J. Pink, et al (2017) Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. *BMC Infectious Diseases*. <https://doi.org/10.1186/s12879-017-2301-4>
22. L. Ge, Jichun Ma, Min Han, et al (2014) Interferon- γ Release Assay for the Diagnosis of Latent *Mycobacterium tuberculosis* Infection in Children Younger Than 5 Years. *La Clinica pediatrica*. <https://doi.org/10.1177/0009922814540040>

23. S. Machingaidze, C. Wiysonge, Y. Gonzalez-Angulo, et al (2011) The Utility of an Interferon Gamma Release Assay for Diagnosis of Latent Tuberculosis Infection and Disease in Children: A Systematic Review and Meta-analysis. The Pediatric Infectious Disease Journal. <https://doi.org/10.1097/INF.0b013e318214b915>
24. J. Campbell, Jane Krot, K. Elwood, et al (2015) A Systematic Review on TST and IGRA Tests Used for Diagnosis of LTBI in Immigrants. Molecular Diagnosis & Therapy. <https://doi.org/10.1007/s40291-014-0125-0>
25. Wenjin Wang, Aohan Liu, Xinjie Liu, et al (2024) Mycobacterium tuberculosis Infection in School Contacts of Tuberculosis Cases: A Systematic Review and Meta-Analysis. American Journal of Tropical Medicine and Hygiene. <https://doi.org/10.4269/ajtmh.23-0038>
26. Mohammad Mohammadi, Narges Norouzkhani, Motahare Rouhparvarzamin, et al (2025) Diagnosing nontuberculous mycobacterial cervicofacial lymphadenitis in children: An updated systematic review. Microbes and Infectious Diseases. <https://doi.org/10.21608/mid.2025.324731.2256>
27. S. Willemse, M. Oomens, J. Lange, L. Karssemakers (2018) Diagnosing nontuberculous mycobacterial cervicofacial lymphadenitis in children: A systematic review. International Journal of Pediatric Otorhinolaryngology. <https://doi.org/10.1016/j.ijporl.2018.06.034>
28. E. S. Saba, G. Ansari, Jacob E. Hoerter, et al (2023) The diagnosis of nontuberculous cervicofacial lymphadenitis: A systematic review. American Journal of Otolaryngology. <https://doi.org/10.1016/j.amjoto.2023.104030>
29. M. Jeljeli, V. Guérin-El Khourouj, V. Pommelet, et al (2017) Cytokine/chemokine secretion for detecting tuberculosis in quantiferon supernatants from HIV+ and HIV- children. Journal of Infection. <https://doi.org/10.1016/j.jinf.2017.04.009>

30. N. Korneva, Anastasiya Vtulkina, Christina Kazarina, et al (2019) Discrepancy between the results of immunological tests in children with tuberculosis infection. *Tuberculosis*. <https://doi.org/10.1183/13993003.congress-2019.pa3631>
31. J. Calzada-Hernández, Jordi Antón, Esmeralda Núñez, et al (2015) THU0513 Diagnosis of Tuberculosis Infection in Pediatric Patients Treated with Tumor Necrosis Factor Alpha Inhibitors; A Multicenter Spanish Study Comparing IGRA and Tuberculin Skin Tests. <https://doi.org/10.1136/annrheumdis-2015-eular.6373>
32. C. Leung, K. Chang (2009) Role of interferon gamma release assays in tuberculosis. *Respirology (Carlton South Print)*. <https://doi.org/10.1111/j.1440-1843.2008.01470.x>
33. Amita Gupta, Priya Singh, L. Aaron, et al (2023) Timing of maternal isoniazid preventive therapy on tuberculosis infection among infants exposed to HIV in low-income and middle-income settings: a secondary analysis of the TB APPRISE trial. *The Lancet Child & Adolescent Health*. [https://doi.org/10.1016/s2352-4642\(23\)00174-8](https://doi.org/10.1016/s2352-4642(23)00174-8)
34. A. Starshinova, Irina Dovgaluk, U. Ovchinnikova, et al (2017) Features of immunological parameters in children with generalized tuberculosis. <https://doi.org/10.1183/1393003.congress-2017.pa2752>
35. M. Kakinda, R. Olum, J. Baluku, F. Bongomin (2023) Diagnostic accuracy of clinical diagnostic scoring systems for childhood tuberculosis: a systematic review and meta-analysis protocol. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2022-069448>
36. Guozhong Zhou, Qingyi Luo, Shiqi Luo, et al (2020) Interferon- γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infectious Diseases (Print)*. [https://doi.org/10.1016/s1473-3099\(20\)30276-0](https://doi.org/10.1016/s1473-3099(20)30276-0)

37. C. Oh, E. Ortiz-Brizuela, M. Bastos, D. Menzies (2020) Comparing the Diagnostic Performance of QFT-Plus to Other Tests of Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. *Clinical Infectious Diseases*. <https://doi.org/10.1093/cid/ciaa1822>
38. L. Slogotskaya, Elena Bogorodskaya, M. Sinitsyn, et al (2020) Screening for TB infection in children using skin tests with tuberculin and recombinant allergen (CFP-10-ESAT-6). <https://doi.org/10.1183/13993003.congress-2020.2809>
39. N. Korneva, G. Balasaniantc, M. Yakovleva, et al (2019) Study of the tuberculosis activity at spontaneously cured children using skin test with tuberculous recombinant allergen. *Tuberculosis*. <https://doi.org/10.1183/13993003.congress-2019.pa3625>
40. Naglaa Fathy Abd Elrazik Ibrahim, S. Mansour, Ehab Hamed Abd Elsalam, R. Rabie (2021) Study of Latent Tuberculosis among Type 1 Diabetic Children in Zagazig University Pediatric Hospital. *The Egyptian Journal of Hospital Medicine*. <https://doi.org/10.21608/ejhm.2021.180970>
41. P. Auguste, A. Tsertsvadze, J. Pink, et al (2016) Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation. *Health Technology Assessment*. <https://doi.org/10.3310/hta20380>
42. E. D. Keyser, F. Keyser, F. Baets (2014) Tuberculin skin test versus interferon-gamma release assays for the diagnosis of tuberculosis infection. <https://doi.org/10.1179/2295333714Y.0000000043>
43. Ratih Pasande (2023) SCREENING FOR TUBERCULOSIS DISEASE AMONG CHILDREN: A SYSTEMATIC REVIEW. *Journal of Advance Research in Medical & Health Science* (ISSN: 2208-2425). <https://doi.org/10.53555/nmhs.v9i9.1838>

44. L. Fan, Zhou Chen, X. Hao, et al (2012) Interferon-gamma release assays for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *FEMS Immunology & Medical Microbiology*. <https://doi.org/10.1111/j.1574-695X.2012.00972.x>
45. Inga Dekerytė, A. Lukošiušė-Urbonienė, Kamile Donielaite-Anise, et al (2021) Peritoneal Tuberculosis in Children Over the Last Decade: A Systematic Literature Review. <https://doi.org/10.21203/rs.3.rs-244806/v1>
46. P. Siddhi, R. Raveendranath, A. Chinnaswamy, et al (2022) A systematic review on correlates of risk of TB disease in children and subjects. *Indian Journal of Tuberculosis*. <https://doi.org/10.21203/rs.3.rs-1261861/v1>
47. Luis E. Cuevas, L. M. Almeida, P. Mazunder, et al (2002) Effect of zinc on the tuberculin response of children exposed to subjects with smear-positive tuberculosis. *Annals of Tropical Paediatrics*. <https://doi.org/10.1179/027249302125001967>
48. N. Korneva, A. Starshinova, Julia Ovchinnikova, et al (2014) Immune response in children with latent tuberculosis infection and active pulmonary tuberculosis
49. Ş. Bozdemir, S. Çelebi, M. Hacımustafaoğlu, et al (2011) Evaluation of Tuberculin Skin Test Results of One Year. <https://doi.org/10.5152/ced.2011.44>
50. Mingjie Yu, Wei Zhu, D. Liang, Yanzhen Li (2014) Screening situation analysis on children aged 0 to 14 in close contact to patients with smear-positive pulmonary tuberculosis. <https://doi.org/10.3760/CMA.J.ISSN.1007-1245.2014.21.011>
51. E. C. Pearce, Jason Woodward, W. Nyandiko, et al (2012) A Systematic Review of Clinical Diagnostic Systems Used in the Diagnosis of Tuberculosis in Children. *AIDS Research and Treatment*. <https://doi.org/10.1155/2012/401896>

52. T. Togun, E. MacLean, B. Kampmann, M. Pai (2018) Biomarkers for diagnosis of childhood tuberculosis: A systematic review. PLoS ONE. <https://doi.org/10.1371/journal.pone.0204029>
53. M. Kakinda, R. Olum, J. Baluku, F. Bongomin (2023) Diagnostic Accuracy of Clinical Diagnostic Scoring Systems for Childhood Tuberculosis: A Systematic Review and Meta-analysis. Open Forum Infectious Diseases. <https://doi.org/10.1093/ofid/ofad624>
54. A. Starshinova, Dmitriy Kudliy, Irina Dovgaluk (2020) Efficacy of Russian immunologic skin test recombinant allergen Diaskintest - ten years (meta-analysis data). <https://doi.org/10.1183/13993003.congress-2020.2813>
55. P. Auguste, J. Madan, A. Tsertsvadze, et al (2019) Identifying latent tuberculosis in high-risk populations: systematic review and meta-analysis of test accuracy. The International Journal of Tuberculosis and Lung Disease. <https://doi.org/10.5588/ijtld.18.0743>
56. R. Diel, R. Loddenkemper, A. Nienhaus (2012) Predictive value of interferon- γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest. <https://doi.org/10.1378/chest.11-3157>
57. C. Greenaway, M. Pareek, C. A. Abou Chakra, et al (2018) The effectiveness and cost-effectiveness of screening for latent tuberculosis among migrants in the EU/EEA: a systematic review. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. <https://doi.org/10.2807/1560-7917.ES.2018.23.14.17-00543>
58. J. Uzorka, J. Wallinga, L. Kroft, et al (2019) Radiological Signs of Latent Tuberculosis on Chest Radiography: A Systematic Review and Meta-Analysis. Open Forum Infectious Diseases. <https://doi.org/10.1093/ofid/ofz313>

59. B. Ukoaka, Faithful Miebaka Daniel, P. Wagwula, et al (2024) Prevalence, clinical characteristics, and treatment outcomes of childhood tuberculosis in Nigeria: a systematic review and meta-analysis. BMC Infectious Diseases. <https://doi.org/10.1186/s12879-024-10321-3>
60. K. Gunasekera, O. Marcy, Johanna Muñoz, et al (2023) Development of treatment-decision algorithms for children evaluated for pulmonary tuberculosis: an individual participant data meta-analysis. The Lancet Child & Adolescent Health. [https://doi.org/10.1016/S2352-4642\(23\)00004-4](https://doi.org/10.1016/S2352-4642(23)00004-4)
61. X. Qiu, Y. Tang, Y. Yue, et al (2019) Accuracy of interferon- γ -induced protein 10 for diagnosing latent tuberculosis infection: a systematic review and meta-analysis. Clinical Microbiology and Infection. <https://doi.org/10.1016/j.cmi.2018.12.006>
62. Yu Zhang, Guozhong Zhou, Wei Shi, et al (2023) Comparing the diagnostic performance of QuantiFERON-TB Gold Plus with QFT-GIT, T-SPOT.TB and TST: a systematic review and meta-analysis. BMC Infectious Diseases. <https://doi.org/10.1186/s12879-023-08008-2>
63. H. Mayanja-Kizza, A. Katamba (2020) Interferon- γ release assays or tuberculin skin test for latent tuberculosis infection? Lancet Infectious Diseases (Print). [https://doi.org/10.1016/s1473-3099\(20\)30363-7](https://doi.org/10.1016/s1473-3099(20)30363-7)
64. Tsabita Hadid, Muhammad Faris, Betty Agustina Tambunan (2023) TUBERCULIN SKIN TEST AND INTERFERON- γ RELEASE ASSAY ON THE DIAGNOSIS OF TUBERCULOUS SPONDYLITIS. Majalah Biomorfologi. <https://doi.org/10.20473/mbiom.v33i2.2023.92-99>
65. Y. Hamada, Rishi K. Gupta, Matteo Quartagno, et al (2023) Predictive performance of interferon-gamma release assays and the tuberculin skin test for incident tuberculosis: an individual participant data meta-analysis. EClinicalMedicine. <https://doi.org/10.1016/j.eclinm.2022.101815>
66. C. Lange, Martina Sester, G. Sotgiu, et al (2011) Interferon- γ release assays for diagnosis of active pleural tuberculosis: a developing world perspective. European Respiratory Journal. <https://doi.org/10.1183/09031936.00071111>

67. Manvi Singh, N. Jaiswal, Shreya Singh, et al (2020) Prevalence of Latent Tuberculosis in Contacts of Pulmonary Tuberculosis patients: A Systematic Review and Meta-Analysis. <https://doi.org/10.22541/au.160258688.83214602/v1>
68. E. Bunyasi, B. Schmidt, L. Abdullahi, et al (2017) Prevalence of latent TB infection and TB disease among adolescents in high TB burden countries in Africa: a systematic review protocol. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2016-014609>
69. G. Jaffe, P. Larson, A. Haugh, Gretchen Shelesky (2020) In teenagers with acute pharyngitis, do steroids shorten the duration of symptoms? <https://doi.org/10.1097/ebp.0000000000000808>
70. Hiu Ying Joanna Choi, Jamie Hill-Daniel (2020) Do interferon-gamma release assays have better sensitivity and specificity than the TST for the diagnosis of active tuberculosis in high-risk populations? <https://doi.org/10.1097/EBP.0000000000000814>
71. Jiaru Yang, Zhenhua Ji, Yu Zhang, et al (2020) Predictive performance of interferon- γ release assays and tuberculin skin tests - Authors' reply. *Lancet Infectious Diseases* (Print). [https://doi.org/10.1016/s1473-3099\(20\)30872-0](https://doi.org/10.1016/s1473-3099(20)30872-0)
72. El Kabeer, MN Seddek, E. Tayeb, El Ridi (2011) Evaluation of Serological Tests for Immunodiagnosis of Pulmonary Tuberculosis using A60 and Lipoarabinomannan Antigens. <https://doi.org/10.21608/besps.2011.36121>
73. R. Subramani, M. Datta, S. Swaminathan (2015) Does effect of BCG vaccine decrease with time since vaccination and increase tuberculin skin test reaction? *Indian Journal of Tuberculosis*. <https://doi.org/10.1016/j.ijtb.2015.08.002>
74. A. Mohammad, O. Mohammad, A. Shoman (2015) Comparative study between tuberculin skin test and serum albumin level in patients with active pulmonary tuberculosis. <https://doi.org/10.4103/1687-8426.158086>

75. J. Pyo, Y. Sung (2013) AB0726 Systemic review: agreement between tuberculin skin test (TST) and-gamma release assay (IGRA) blood test for latent tb screening among patients with rheumatic diseases. <https://doi.org/10.1136/annrheumdis-2013-eular.3048>