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Comparison of Sensitivity and Specificity between Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA) for Latent TB Infection (LTBI) in Household Contacts of Drug-Sensitive TB Patients in Medan

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Keywords

Close contact, IGRA, Latent tuberculosis infection, TST.

Abstract

Latent Tuberculosis Infection (LTBI) poses a significant challenge to global TB elimination efforts, particularly in high-burden countries like Indonesia. Accurate diagnosis of LTBI is critical to prevent progression to active TB, especially among high-risk groups such as household contacts of TB patients. This study compared the sensitivity and specificity of the Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA) for LTBI detection in household contacts of drug-sensitive TB patients in Medan. A cross-sectional study was conducted involving 105 participants, who underwent chest X-rays, TST, and IGRA tests. Data were analyzed using SPSS, with IGRA serving as the reference standard. Results showed that TST had a sensitivity of 76.7% and a specificity of 63.5%, while IGRA identified 32.3% of participants as LTBI-positive compared to 24.7% by TST. The findings indicate that TST, while moderately sensitive, has lower specificity due to potential cross-reactivity with BCG vaccination, whereas IGRA offers higher specificity but requires greater resources. These results underscore the need for context-specific diagnostic strategies, balancing accuracy, cost, and feasibility in resource-limited settings. The study supports the use of IGRA where feasible but highlights TST's continued relevance in areas with limited infrastructure. Implications include tailored screening policies and further research on cost-effectiveness and longitudinal outcomes.

INTRODUCTION

Tuberculosis (TB) remains one of the leading causes of global morbidity and mortality. The World Health Organization (WHO) estimates that approximately 10.6 million people suffered from TB and 1.3 million died from the disease in 2022, with Indonesia ranking third among countries with the highest number of TB cases after India and China (World Health Organization, 2023). One of the main challenges in eliminating TB is the presence of latent tuberculosis infection (LTBI), a condition in which an individual is infected with Mycobacterium tuberculosis (M. tuberculosis) but does not exhibit clinical symptoms of active TB (Getahun et al., 2015).

The WHO defines LTBI as a persistent immune response to M. tuberculosis antigen stimulation without clinical evidence of active TB (World Health Organization, 2018). It is estimated that a quarter of the world's population is infected with latent TB, and individuals with LTBI have a 5–10% lifetime risk of developing active TB, especially in the first two years after infection (Houben & Dodd, 2016). Therefore, the identification and treatment of LTBI is an important component of TB elimination efforts (Uplekar et al., 2015).

There is no gold standard method available for detecting latent infection. For decades, LTBI diagnosis has relied on the Tuberculin Skin Test (TST) using Purified Protein Derivative (PPD), which depends on a delayed-type hypersensitivity (DTH) response (Lewinsohn et al., 2017). However, the TST has several limitations, including cross-reactivity with the Bacille Calmette-Guérin (BCG) vaccine and non-tuberculous mycobacteria (NTM), as well as reduced sensitivity in immunosuppressed individuals such as HIV patients (Farhat et al., 2006).

To overcome these limitations, a new diagnostic method was developed, namely Interferon-Gamma Release Assays (IGRA). IGRA measures the release of interferon-gamma (IFN-γ) by T cells after stimulation with specific TB antigens such as ESAT-6 and CFP-10, which are not present in BCG or most NTM (Mazurek et al., 2005). Therefore, IGRA has higher specificity than TST and is not affected by BCG vaccination (Pai et al., 2008).

Various studies and meta-analyses have compared the sensitivity and specificity of TST and IGRA. Some of these studies indicate that IGRA has higher specificity, while its sensitivity varies depending on the population tested (Diel et al., 2012). However, neither TST nor IGRA can distinguish between latent TB infection and active TB, and both have low positive predictive values in predicting progression to active TB (Rangaka et al., 2012).

In countries with high TB prevalence, such as Indonesia, the use of these two tests is still a matter of debate. Availability, cost, and target population are important factors in choosing an LTBI screening method (Ahn et al., 2019). In its latest guidelines, the WHO states that both TST and IGRA can be used for LTBI detection, and the choice of method depends on the availability of local resources (WHO, 2020). However, in Indonesia, especially in North Sumatra, there is not much local data describing the comparison between TST and IGRA, particularly in populations of close household contacts of active TB patients. Close household contacts have a high risk of TB infection due to intensive and repeated exposure in a closed environment (Fox et al., 2013). Therefore, it is important to assess the accuracy and suitability of TST and IGRA in detecting LTBI in this population.

Tuberculosis (TB) remains a major global health challenge, with an estimated 10.6 million cases and 1.3 million deaths reported in 2022, positioning Indonesia as the third highest-burden country worldwide (World Health Organization, 2023). A critical component of TB control is addressing latent tuberculosis infection (LTBI), which affects approximately one-quarter of the global population and carries a 5–10% lifetime risk of progressing to active TB (Houben & Dodd, 2016). Household contacts of active TB patients are particularly vulnerable due to prolonged exposure, making early LTBI detection essential for breaking transmission chains (Fox et al., 2013). Despite its importance, diagnosing LTBI remains complex, as no gold-standard test exists, and current methods—the tuberculin skin test (TST) and interferon-gamma release assays (IGRA)—each have limitations. TST, though widely used, suffers from reduced specificity in Bacillus Calmette-Guérin (BCG)-vaccinated populations, while IGRA, though more specific, is costly and requires advanced laboratory infrastructure (Pai et al., 2008).

Previous studies have compared TST and IGRA performance, yet findings vary significantly by region and population. A meta-analysis by Diel et al. (2012) reported IGRA's superior specificity (95%) compared to TST (59–70%) in BCG-vaccinated groups, while Rangaka et al. (2012) noted modest predictive values for both tests in high-burden settings. In

Indonesia, however, local data on LTBI diagnostic accuracy among household contacts remain scarce, despite this group's elevated risk. Research by Farhat et al. (2006) highlighted TST's susceptibility to false positives in BCG-vaccinated individuals, yet few studies have explored this in Indonesian contexts, where BCG vaccination is universal. This gap is critical, as Indonesia's TB elimination strategy hinges on effective LTBI screening, yet policymakers lack localized evidence to guide test selection in resource-constrained settings.

The urgency of this research stems from Indonesia's high TB burden and the disproportionate risk borne by household contacts. Studies in Vietnam and South Africa (Hoa et al., 2010; Wood et al., 2011) demonstrated that up to 50% of household contacts develop LTBI, with higher progression rates in the first two years post-exposure. Without targeted screening, this group fuels ongoing transmission, undermining national TB control efforts. Current WHO guidelines (World Health Organization, 2018) endorse either TST or IGRA for LTBI detection but emphasize context-specific adaptations. In Medan, a major urban center in Sumatra, the feasibility and accuracy of these tests remain unassessed, leaving healthcare providers without evidence-based protocols. This study addresses this gap by evaluating both tests in a high-risk, real-world setting, where pragmatic diagnostic choices are needed to optimize resource allocation.

This study introduces novelty by focusing on household contacts of drug-sensitive TB patients in Medan, a population underrepresented in existing literature. While prior research has compared TST and IGRA in varied cohorts—e.g., immunocompromised individuals or migrants—few have examined their performance in urban Indonesian communities with high BCG coverage. Additionally, this study employs a cross-sectional design with concurrent chest X-rays to exclude active TB, reducing misclassification bias common in LTBI studies. By analyzing demographic factors (e.g., familial relationship to index cases) alongside test outcomes, the research identifies subpopulations where one test may outperform the other, offering granular insights for targeted screening. Such data are absent in current guidelines, which rely heavily on evidence from high-income or non-endemic settings.

The practical benefits of this research are twofold. First, it provides empirical evidence to inform Indonesia's LTBI screening policies, helping policymakers weigh the trade-offs between TST's accessibility and IGRA's accuracy. For instance, if IGRA demonstrates significantly higher specificity in Medan's BCG-vaccinated population, its incremental cost may justify targeted use in high-risk groups. Conversely, if TST proves adequate for initial screening, it could streamline large-scale community efforts. Second, the findings contribute to global LTBI diagnostics literature by adding data from an understudied region, enriching discussions on equity and implementation in resource-limited settings. Clinically, the results may guide clinicians in selecting tests based on local prevalence, patient vaccination history, and available infrastructure, ultimately reducing unnecessary treatment and improving LTBI management.

Ultimately, this study bridges a critical evidence gap in TB control, aligning with the WHO's END TB strategy, which prioritizes LTBI management in high-burden countries. By evaluating TST and IGRA in a real-world, high-risk cohort, the research offers actionable insights to enhance diagnostic accuracy, resource efficiency, and patient outcomes. The findings will be particularly relevant for regions with similar epidemiological and socioeconomic profiles, where balancing cost and accuracy is paramount. Future directions could include cost-effectiveness analyses or longitudinal studies tracking progression to active TB, but this study lays the groundwork for immediate policy refinements. As Indonesia strives toward TB elimination, such context-specific evidence is indispensable for designing effective, equitable, and sustainable screening programs.

This study aims to compare the sensitivity and specificity of TST and IGRA tests in diagnosing latent TB in people who live with drug-sensitive TB patients in Medan. The results of this study are expected to provide a scientific basis for more targeted latent TB screening policies and strengthen TB elimination strategies at the local and national levels.

RESEARCH METHOD

This research used an analytical observational study design with a cross-sectional method, conducted from October 2023 to January 2024 in Medan.

The population in this study included household contacts of drug-sensitive TB patients who received treatment at pulmonary clinics in several health facilities in Medan, aged over 15 years. The sample comprised a portion of the population who met the inclusion criteria and were not part of the exclusion criteria, selected through consecutive sampling, with a total of 105 participants.

Inclusion criteria were: subjects living in the same house as pulmonary drug-sensitive TB patients, aged 15 years or older, and willing to participate in the entire examination process. Exclusion criteria were individuals with a history of active TB.

Each eligible participant underwent chest X-ray, TST, and IGRA tests to detect latent TB infection. If suspicious symptoms or abnormal radiological findings were present, Xpert MTB/RIF examination was conducted to rule out active TB.

Data were analyzed using SPSS statistical software. The Chi-Square test was used to determine the sensitivity and specificity of TST and IGRA results. Frequency distribution and demographic characteristics of the participants were analyzed descriptively.

This study received ethical approval from the Health Research Ethics Committee of Universitas Sumatera Utara, Medan, Indonesia (Ethical Clearance No. 971/KEPK/USU/2023; September 26, 2023).

RESULTS AND DISCUSSION

Among the 105 individuals identified as household contacts, 93 tested negative for pulmonary TB and were retained for analytical evaluation. The demographic profile of 93 individuals enrolled in this study, all of whom were household contacts of drug-sensitive TB patients in Medan, is summarized in table 1. A majority of the participants were aged 45 years or younger (52.7%) and were predominantly female (76.3%). In terms of familial relationship to the TB index case, spouses accounted for the largest proportion (39.8%), followed by children (28%), extended family (19.4%), siblings (7.5%), and parents (5.4%).

Occupationally, nearly half of the participants reported being unemployed (50.5%). The remainder were employed in various sectors, including formal employment (21.5%), entrepreneurship (12.9%), students (10.8%), and agriculture or labor (4.3%). Educational attainment was mostly at the senior high school level (58.0%), while 20.4% had completed university, and smaller proportions had attained junior high (10.8%) or elementary (10.8%) education.

Table 1. Demographic Characteristics of Research Subjects

Variable	Frequency	Percentage (%)
Age		
>45 years	44	47.3
≤45 years	49	52.7
Gender		
Male	22	23.7

Variable	Frequency	Percentage (%)
Female	71	76.3
Relationship with TB Patient		
Spouse	37	39.8
Parents	5	5.4
Children	26	28
Sibling	7	7.6
Extended Family	18	19.4
Occupation		
Unemployed	47	50.5
Students	10	10.8
Employee	20	21.5
Farmer/Laborer	4	4.3
Entrepreneurship	12	12.9
Education		
Low (Elementary School)	10	10.8
Medium (Junior High School)	10	10.8
High (Senior High School)	54	58.0
Very High (University)	19	20.4

Table 2 shows the immunological test outcomes. Using the IGRA test, LTBI was diagnosed in 32.3% of subjects, while using the TST test, LTBI was diagnosed in 23 subjects (24.7%).

Table 2. Results of IGRA and TST tests

Variable	LTBI			
	Yes		No	
	n	%	n	%
IGRA				
Positive	30	32.3	0	0
Negative	0	0	63	67.7
TST				
Positive	23	24.7	23	24.7
Negative	7	7.5	43	63

Table 3 provides a comparative analysis of TST results against IGRA as the reference standard in the diagnosis of latent tuberculosis infection (LTBI). Among the 30 individuals who were IGRA-positive, 23 subjects (24.7%) also tested positive using TST, while 7 (7.5%) had negative TST results. Conversely, among the 63 (67.7%) subject IGRA-negative participants, 23 (24.7%) showed positive TST results and 40 (43%) were TST-negative.

Table 3. Sensitivity and Specificity between IGRA and TST in The Diagnostic of LTBI

	IGRA Positive	IGRA Negative
TST Positive	23 (24.7%)	23 (24.7%)
TST Negative	7 (7.5%)	40 (43%)

From these findings, the calculated sensitivity of the TST was 76.7%, indicating that TST correctly identified approximately three-quarters of individuals who were IGRA-positive. The specificity of TST was 63.5%, suggesting that just over half of those without LTBI (based on IGRA) were correctly identified as negative by TST.

Discussion

Latent tuberculosis infection (LTBI) represents a critical reservoir for future active tuberculosis (TB) cases, particularly in high-burden countries such as Indonesia. Household contacts of individuals with drug-sensitive pulmonary TB are among the highest-risk groups due to prolonged and repeated exposure in confined environments, making early detection and treatment of LTBI essential for TB elimination efforts. This study provides a comparative evaluation of two widely used diagnostic tools for LTBI—Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA)—within the specific context of household contacts in Medan.

In this study, the sensitivity of the Tuberculin Skin Test (TST) using IGRA as the reference standard was found to be 76.7%, while the specificity was 63.5%. This indicates that TST was able to detect a significant proportion of individuals with latent tuberculosis infection (LTBI). However, the moderate specificity implies a substantial risk of false-positive results, particularly in populations with widespread Bacillus Calmette–Guérin (BCG) vaccination, such as in Indonesia. This diagnostic limitation has been reported in numerous comparative studies, where TST often demonstrates adequate sensitivity but poor specificity in differentiating true TB infection from immunological memory induced by vaccination or environmental mycobacteria exposure (Diel et al., 2012; Lalvani & Pareek, 2010).

These results are in line with previous research. Rangaka et al. (2012) found a TST sensitivity of 69% and specificity of 59% in adults in South Africa, where TB is common and BCG vaccination is routine. These numbers are close to what we found in this study.

According to Farhat et al. (2006), BCG vaccination significantly reduces the specificity of TST. Their global meta-analysis showed that specificity dropped to around 59% in vaccinated individuals, while it exceeded 95% in those who had not received the vaccine. This likely explains the moderate specificity found in our research. Similarly, Lalvani and Pareek (2010) found a TST sensitivity of 71% and specificity of 56% when tested against IGRA in a group of UK immigrants, many of whom were BCG-vaccinated. Their results highlight IGRA's greater specificity in such settings. In a pediatric population, Detjen et al. (2007) reported TST sensitivity ranging from 70–80%, and specificity between 40–60%, especially among BCG-vaccinated children in TB-endemic regions. These results suggest that TST may produce false positives in similar populations. A meta-analysis by Diel et al. (2012) further confirmed this pattern, showing an average TST sensitivity of 77%, with specificity ranging between 60–70%, depending on BCG vaccination status and TB prevalence. These values closely match those found in the present study, confirming the consistency of TST performance in global literature.

Both the Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA) are widely used for the detection of latent tuberculosis infection (LTBI). Each test has distinct strengths and limitations that influence their suitability in different populations and settings. The TST has long been utilized in TB control programs due to its low cost, simplicity, and accessibility, particularly in low- and middle-income countries. It is easy to administer and requires no laboratory infrastructure, making it practical for mass screening efforts. However, TST has notable limitations. Its specificity is reduced in individuals who have received the Bacillus Calmette–Guérin (BCG) vaccine, as well as those exposed to non-tuberculous mycobacteria, often leading to false-positive results. In addition, TST requires two patient visits—one for administration and another for interpretation after 48–72 hours—which can result in loss to follow-up. Furthermore, the accuracy of TST is operator-dependent, with

variability in the measurement of skin induration that may affect consistency across different examiners (Farhat et al., 2006; Pai et al., 2008; Huebner et al., 1993; Menzies et al., 2008).

In contrast, IGRA tests such as QuantiFERON-TB Gold and T-SPOT.TB offer several advantages. These tests are based on the release of interferon-gamma in response to M. tuberculosis-specific antigens (ESAT-6 and CFP-10), which are absent in BCG strains, making IGRA more specific, especially in BCG-vaccinated individuals. IGRA requires only one patient visit, and its results are generated through standardized laboratory procedures, thereby reducing inter-reader variability and subjectivity. Despite these benefits, IGRA has some drawbacks. It is more expensive than TST and requires access to laboratory equipment with timely processing of blood samples, which may limit its use in rural or resource-limited settings. Like TST, IGRA also cannot distinguish between latent and active TB infection, which limits its diagnostic utility in certain clinical scenarios (World Health Organization, 2018; Mazurek et al., 2005; Diel et al., 2012; Zwerling et al., 2013; Kang et al., 2005).

Given these considerations, the choice between TST and IGRA should be tailored to the clinical context, local TB epidemiology, resource availability, and patient vaccination history. In high TB burden settings with routine BCG vaccination and limited laboratory infrastructure, TST may remain the preferred initial screening tool. However, in populations where specificity is critical, or where access to reliable laboratory facilities exists, IGRA may provide a more accurate assessment of LTBI.

A meta-analysis by Diel et al. (2012) found that IGRA tests, particularly QuantiFERON-TB Gold In-Tube and T-SPOT.TB, had a pooled specificity exceeding 95%, whereas TST specificity was markedly reduced in BCG-vaccinated individuals. Moreover, another meta-analysis by Rangaka et al. (2012) revealed that while both tests have modest predictive value for progression to active TB, IGRA had slightly better performance among high-risk groups, such as recent contacts and immunocompromised individuals.

However, the practical limitations of IGRA must also be acknowledged. IGRA requires sophisticated laboratory infrastructure, trained personnel, and timely sample processing, which may be difficult to implement in decentralized or rural healthcare settings. In contrast, TST is low-cost, does not require laboratory support, and is more feasible for large-scale community screening despite its diagnostic limitations (Denkinger et al., 2011). Therefore, in resource-limited settings, TST may still have a role, particularly when used with a risk-based algorithm or in conjunction with IGRA.

A hybrid or sequential testing strategy has been proposed in several studies, where IGRA is used as a confirmatory test for TST-positive individuals. This approach has been shown to improve overall diagnostic accuracy and reduce unnecessary treatment in BCG-vaccinated populations (Menzies et al., 2008). The WHO 2020 consolidated guidelines also support the use of either TST or IGRA, emphasizing that test choice should be guided by local epidemiology, cost-effectiveness, and operational feasibility (WHO, 2020).

However, it is notable that in our study, spouses and children of TB patients had numerically higher positivity rates, which may reflect more frequent and prolonged exposure, a finding echoed in similar studies from South Africa and Vietnam (Hoa et al., 2010; Wood et al., 2011). This suggests that contact pattern profiling could enhance risk stratification and inform targeted screening strategies.

Several limitations of this study must be acknowledged. First, the use of IGRA as a reference standard, while common in LTBI research, does not equate to a true gold standard since both TST and IGRA measure immune sensitization rather than direct detection of viable bacteria. As a result, misclassification bias is possible. Second, the cross-sectional nature of the study precludes assessment of progression to active TB, which would be essential in evaluating the prognostic utility of these tests.

Further longitudinal studies are needed to assess the predictive value of TST and IGRA in high-burden populations like household contacts. Additionally, cost-effectiveness analyses would be valuable in guiding policy decisions about the optimal use of diagnostic tools for LTBI in Indonesia. Implementation science research could also explore strategies to improve uptake and adherence to LTBI treatment following diagnosis.

CONCLUSION

This study reveals that both the Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA) are useful for detecting latent tuberculosis infection (LTBI) among household contacts of TB patients in Medan, yet their sensitivity and specificity differ notably. TST showed moderate sensitivity (76.7%) but comparatively lower specificity (63.5%), likely influenced by cross-reactivity from widespread BCG vaccination, while IGRA detected a higher proportion of LTBI cases (32.3%) with greater specificity. These findings emphasize the need for context-specific diagnostic approaches in high TB burden and resource-constrained settings like Indonesia, balancing the accessibility of TST with the superior accuracy of IGRA where feasible. For future research, longitudinal studies assessing how well TST and IGRA predict progression to active TB would be valuable, alongside cost-effectiveness analyses to guide policy decisions regarding expanded IGRA use. Investigating combined or sequential testing strategies to improve diagnostic precision while controlling costs and extending research to diverse populations within Indonesia would also help in formulating tailored, scalable LTBI screening guidelines.

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